Lao, MariaLouisa

From: Sharma, Saloni (ASRC)
Sent: Monday, March 26, 2007 10:55 AM
To: Lao, MariaLouisa
Subject: RE: please help - need help on how to search

Hi Louisa,

Here it is!

Surprisingly enough I searched for all 4 structures and CAs only had 4 references for all if these compounds none of which had the keyword METALLOPROTEINASE.

So here is what I did: I searched for the molecular formulas for all 3 compounds and narrowed the set to the above keyword! Below is a description of what you will see in the file:

1. Inventor results 1-44

2 Query results: This contains the molecular formular search and the structure search in registry, and marpat. The 4 compounds of concern that generated only 4 references are numbers 25-28 of L91.

let me know if you have any questions!

Good Luck,

Saloni

20070326-105
69812-str.rtf

-----Original Message-----
From: Lao, MariaLouisa
Sent: Monday, March 26, 2007 9:23 AM
To: Shrestha, Usha (ASRC); Sharma, Saloni (ASRC)
Subject: please help - need help on how to search
Importance: High

Good Morning!
Hi Ladies,

Please provide tips on searching:

1- these compounds

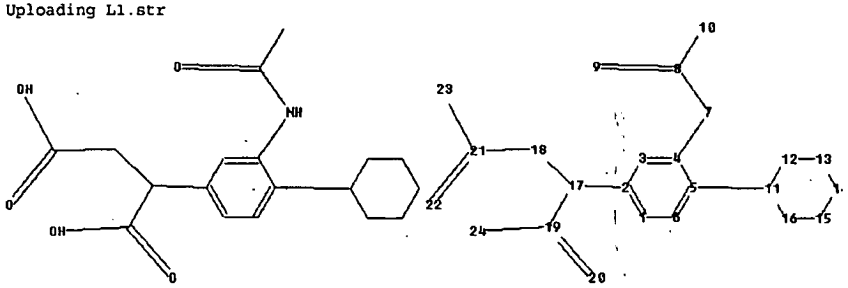
[3-(acetylamino)-4-cyclohexylphenyl]-butanedioic acid
[3-(acetylamino)-4-cyclohexylphenyl]-butanedioic acid
[3-(acetylamino)-4-cyclohexylphenyl]-butanedioic acid diethyl ether
[3-methoxy-4-(phenylmethoxy)phenyl] butanedioic acid

2- also, is /au enough as descriptive suffix to an inventors name - for an STN search?

If you need me to come by - please let me know - I really need to get the above search done within the next two hours.

Thanks.
Louisa

Uploading L1.str



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7 8 9 10 17 18 19 20 21 22 23 24
ring nodes :
1 2 3 4 5 6 11 12 13 14 15 16
chain bonds :
2-17 4-7 5-11 7-8 8-9 8-10 17-18 17-19 18-21 19-20 19-24 21-22 21-23

ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16
exact/norm bonds :
4-7 7-8 8-9 11-12 11-16 12-13 13-14 14-15 15-16
exact bonds :
2-17 5-11 8-10 17-18 17-19 18-21
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 19-20 19-24 21-22 21-23

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS
20:CLASS 21:CLASS
22:CLASS 23:CLASS 24:CLASS

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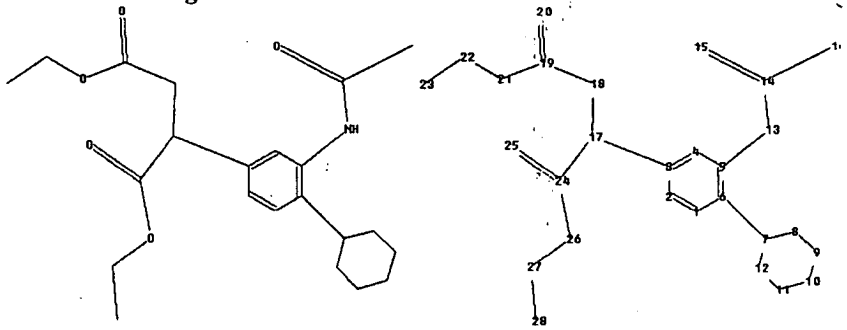

chain nodes :
13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12
chain bonds :
3-17 5-13 6-7 13-14 14-15 14-16 17-18 17-24 18-19 19-20 19-21 21-22 22-23
24-25 24-26 26-27 27-28
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 7-8 7-12 8-9 9-10 10-11 11-12
exact/norm bonds :
5-13 7-8 7-12 8-9 9-10 10-11 11-12 13-14 14-15 19-20 19-21 21-22 24-25 24-26 26-27
exact bonds :
3-17 6-7 14-16 17-18 17-24 18-19 22-23 27-28
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:CLASS 14:CLASS 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS
22:CLASS 23:CLASS 24:CLASS 25:CLASS 26:CLASS 27:CLASS 28:CLASS

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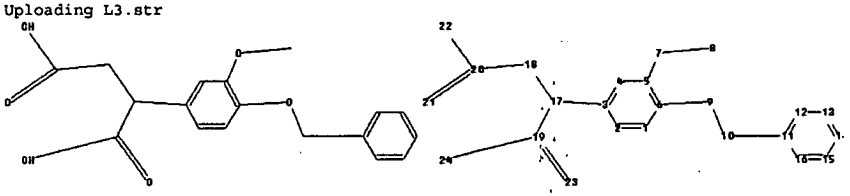

3/26/07

STIC Search

TMH

- Inventor
- Negative Provisos

chain nodes :
7 8 9 10 17 18 19 20 21 22 23 24
ring nodes :
1 2 3 4 5 6 11 12 13 14 15 16
chain bonds :
3-17 5-7 6-9 7-8 9-10 10-11 17-18 17-19 18-20 19-23 19-24 20-21 20-22

ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16
exact/norm bonds :
5-7 6-9 7-8 9-10
exact bonds :
3-17 10-11 17-18 17-19 18-20
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 11-12 11-16 12-13 13-14 14-15 15-16 19-23 19-24
20-21 20-22

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:CLASS 10:CLASS
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS
20:CLASS 21:CLASS
22:CLASS 23:CLASS 24:CLASS

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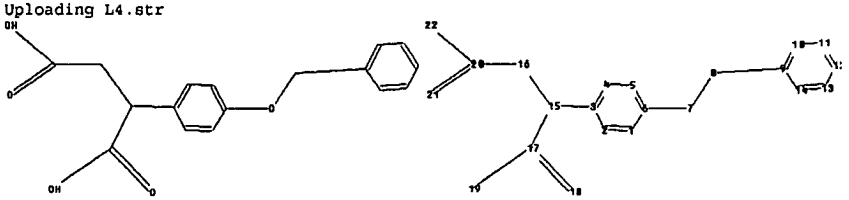

chain nodes :
7 8 15 16 17 18 19 20 21 22
ring nodes :
1 2 3 4 5 6 9 10 11 12 13 14
chain bonds :
3-15 6-7 7-8 8-9 15-16 15-17 16-20 17-18 17-19 20-21 20-22
ring bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14
exact/norm bonds :
6-7 7-8
exact bonds :
3-15 8-9 15-16 15-17 16-20
normalized bonds :
1-2 1-6 2-3 3-4 4-5 5-6 9-10 9-14 10-11 11-12 12-13 13-14 17-18 17-19
20-21 20-22

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:CLASS 8:CLASS 9:Atom 10:Atom

11:Atom 12:Atom 13:Atom 14:Atom 15:CLASS 16:CLASS 17:CLASS 18:CLASS
19:CLASS 20:CLASS 21:CLASS
22:CLASS

**********INVENTOR RESULTS**********

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L3 104 SEA FILE=HCAPLUS ABB=ON PLU=ON ("HOLMES I"/AU OR "HOLMES I B"/AU OR "HOLMES I F"/AU OR "HOLMES I H"/AU OR "HOLMES I P"/AU OR "HOLMES IAN"/AU OR "HOLMES IAN B"/AU OR "HOLMES IAN D"/AU OR "HOLMES IAN F"/AU OR "HOLMES IAN H"/AU OR "HOLMES IAN HAMILTON"/AU OR "HOLMES IAN P"/AU OR "HOLMES IAN PETER"/AU)
L4 99 SEA FILE=HCAPLUS ABB=ON PLU=ON ("WATSON S"/AU OR "WATSON S P"/AU)
L5 164 SEA FILE=HCAPLUS ABB=ON PLU=ON ("WATSON STEFAN"/AU OR "WATSON STEPHEN"/AU OR "WATSON STEPHEN PAUL"/AU OR "WATSON STEPHEN PAUL"/AU OR "WATSON STEVE"/AU OR "WATSON STEVE P"/AU OR "WATSON STEVEN"/AU OR "WATSON STEVEN P"/AU)
L6 263 SEA FILE=HCAPLUS ABB=ON PLU=ON (L4 OR L5)
L7 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND L6
L8 6 SEA FILE=HCAPLUS ABB=ON PLU=ON (L3 OR L4 OR L5) AND METALLOPROTEINASE?
L9 6 SEA FILE=HCAPLUS ABB=ON PLU=ON (L7 OR L8)

=> d que l17
L10 5752 SEA WATSON S?/AU
L11 587 SEA HOLMES I?/AU
L12 8 SEA L10 AND L11
L13 131 SEA (L10 OR L11) AND METALLOPROTEINASE?
L14 97 SEA L13 AND (METALLOPROTEINASE?(L) INHIBIT?)
L15 86 SEA L14 AND (PY<2005 OR AY<2005 OR PRY<2005)
L16 43 DUP REM L15 (43 DUPLICATES REMOVED)
L17 47 SEA (L12 OR L16)

=> dup rem l9,l17
FILE 'HCAPLUS' ENTERED AT 09:49:06 ON 26 MAR 2007
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.
COPYRIGHT (C) 2007 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'MEDLINE' ENTERED AT 09:49:06 ON 26 MAR 2007

FILE 'BIOSIS' ENTERED AT 09:49:06 ON 26 MAR 2007
Copyright (c) 2007 The Thomson Corporation

FILE 'DRUGU' ENTERED AT 09:49:06 ON 26 MAR 2007
COPYRIGHT (C) 2007 THE THOMSON CORPORATION

FILE 'WPIX' ENTERED AT 09:49:06 ON 26 MAR 2007
COPYRIGHT (C) 2007 THE THOMSON CORPORATION

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PROCESSING COMPLETED FOR L9
PROCESSING COMPLETED FOR L17
L18          44 DUP REM L9 L17 (9 DUPLICATES REMOVED)
                ANSWERS '1-17' FROM FILE HCAPLUS
                ANSWERS '18-20' FROM FILE MEDLINE
                ANSWERS '21-32' FROM FILE BIOSIS
                ANSWERS '33-44' FROM FILE DRUGU

=> d ibib abs hitstr retable l18 1-17;d ibib abs l18 18-44

L18  ANSWER 1 OF 44  HCAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER:         2005:260025  HCAPLUS  Full-text
DOCUMENT NUMBER:          142:336245
TITLE:                    Preparation of biphenylpentanoic acid derivatives as
                          matrix metalloproteinase inhibitors
INVENTOR(S):              Gaines, Simon; Holmes, Ian Peter; Martin,
                          Stephen Lewis; Watson, Stephen Paul
PATENT ASSIGNEE(S):       Glaxo Group Limited, UK
SOURCE:                   PCT Int. Appl., 41 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
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     WO 2005026120         A1    20050324    WO 2004-EP10319         20040910
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
             NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
             TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
         RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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             SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
             SN, TD, TG
     AU 2004272280         A1    20050324    AU 2004-272280          20040910
     CA 2538315            A1    20050324    CA 2004-2538315         20040910
     EP 1663970            A1    20060607    EP 2004-765231          20040910
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     CN 1849306            A     20061018    CN 2004-80026229        20040910
     BR 2004013791         A     20061107    BR 2004-13791           20040910
     JP 2007505081         T     20070308    JP 2006-525794          20040910
     NO 2006000540         A     20060404    NO 2006-540             20060202
     US 2006293353         A1    20061228    US 2006-571443          20060313
PRIORITY APPLN. INFO.:                        GB 2003-21538       A   20030913
                                              WO 2004-EP10319     W   20040910

OTHER SOURCE(S):          CASREACT 142:336245; MARPAT 142:336245
GI
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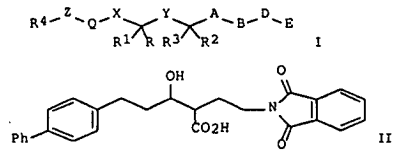

I

II

AB Title compds. represented by the formula I [wherein A = a bond or (CH:CH)alkyl; B = a bond, O, S, SO2, CO, etc.; D = a bond or alkyl; E = (un)substituted (hetero)aryl; Q = (un)substituted (hetero)aryl; X = O, S, SO, SO2, CO, etc.; Y = SO, SO2, CS, etc.; R, R1 = independently H or alkyl(aryl); R2 = carboxy, amido, thiol, etc.; R3 = H or alkyl(aryl); R4 = (un)substituted (hetero)aryl; Z = a bond, CH2, amino, etc., or R4Z = (un)substituted fused tricyclic group; and physiol. functional derivs. thereof] were prepared as matrix *metalloproteinase* (MMP) inhibitors. For example, II was given in a multi-step synthesis starting from biphenyl-4-ylmethanol. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as MMP inhibitors for the treatment of autoimmune disorder or inflammatory condition (no data).

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Refereneed Work (RWK)	Referenced File
Boehringer Ingelheim Ph	2002			WO 02083642 A	HCAPLUS
Brittelli, D	1997			WO 9743238 A	HCAPLUS
Hashizume, H	1994	42	2097	CHEM PHARM BULL	HCAPLUS
Morales, R	2004	341	1063	JOURNAL OF MOLECULAR	HCAPLUS
Natchus, M	2001	44	1060	JOURNAL OF MEDICINAL	HCAPLUS
Squibb Bristol Myers Co	2004			WO 2004012663 A	HCAPLUS

```
L18  ANSWER 2 OF 44  HCAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 2
ACCESSION NUMBER:         2005:158625  HCAPLUS  Full-text
DOCUMENT NUMBER:          142:261292
TITLE:                    Preparation of (hetero)aryl-substituted succinate
                          derivatives as matrix metalloproteinase
                          inhibitors
INVENTOR(S):              Holmes, Ian; Watson, Stephen Paul
PATENT ASSIGNEE(S):       Glaxo Group Limited, UK
SOURCE:                   PCT Int. Appl., 36 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.           KIND   DATE        APPLICATION NO.         DATE
     ---------------      ----   --------    -------------------     --------
     WO 2005016868         A2    20050224    WO 2004-EP9087          20040812
     WO 2005016868         A3    20050519
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             CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,
             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
             LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
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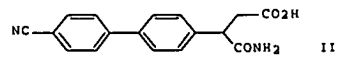
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

EP 1654218	A2	20060510	EP 2004-764084		20040812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR					
JP 2007502259	T	20070208	JP 2006-522996		20040812
US 2006235074	A1	20061019	US 2006-569812		20060210
PRIORITY APPLN. INFO.:			GB 2003-19069	A	20030814
			WO 2004-EP9087	W	20040812

OTHER SOURCE(S): CASREACT 142:261292; MARPAT 142:261292
GI



II

AB Title compds. represented by the formula I, R1ZQCH(R2)CH2X, [wherein R1 = (un)substituted alkyl(cycloalkyl), alkylheterocycloalkyl, alkylaryl, etc.; Z = a bond, CH2, O, S, etc.; Q = (un)substituted (hetero)aryl; X = COR3; R2 = CONH2, CO2H, sulfonylamino, etc.; R3 = OH, oxyalkyl or (un)substituted amino; with a proviso; and physiol. functional derivs. thereof] were prepared as matrix ***metalloproteinase*** (MMP) inhibitors. Coupling reaction of 4-amino-3-(4-bromophenyl)-4-oxobutanoic acid with p-nitrilephenylboronic acid gave II in 100% yield. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as matrix ***metalloproteinase*** inhibitors for the treatment of inflammation or autoimmune disease (no data).

L18 ANSWER 3 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2004:1154657 HCAPLUS Full-text
DOCUMENT NUMBER: 142:56659
TITLE: Preparation of N-arylglycine derivatives and related compounds as inhibitors of matrix ***metalloproteinase***
INVENTOR(S): ***Holmes, Ian; Watson, Stephen Paul***
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 33 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004113279	A1	20041229	WO 2004-EP6553	20040616
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD,				

GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
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NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,
EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG

EP 1636174	A1	20060322	EP 2004-740011		20040616
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR					
JP 2007506664	T	20070322	JP 2006-515980		20040616
US 2006142385	A1	20060629	US 2005-561055		20051216
PRIORITY APPLN. INFO.:			GB 2003-14488	A	20030620
			WO 2004-EP6553	W	20040616

OTHER SOURCE(S): MARPAT 142:56659

AB The invention relates to compds. R1-Z-Q-NR2CH2-X [R1 is optionally substituted alkyl, alkylaryl, aryl or heteroaryl; Z is a bond, CH2, O, S, SO, SO2, NR4, OCR4R5, CR4R5O, or Z, R1 and Q together form an optionally substituted fused tricyclic group; Q is an optionally substituted 5- or 6-membered aryl or heteroaryl ring; X is COR3 or N(OR8)COR9; R2 is SO2R10 or SO2NR10R11; R3 is OR6, NR6R7 or NR6OH; R4, R5 are independently H, alkyl or alkylaryl; R6, R7 are independently H, alkyl or heteroarylalkyl or NR6R7 is a 5- or 6- membered ring which may have one or more addnl. heteroatoms selected from O, S and N; R8-R11 are independently H or alkyl] and physiol. functional derivs., with the exception of N-(ethoxycarbonyl)-N-[4-(1H-tetrazol-1-yl)phenyl]glycine, for use as inhibitors of matrix ***metalloproteinase*** enzymes (MMPs). Thus, p-NCC6H4C6H4-p-N(SO2Me)CH2CO2H was prepared by alkylation of 4-bromoaniline with tert-Bu bromoacetate, followed by methylsulfonylation, ester cleavage (silica gel in toluene at reflux), and reaction with cyanophenylboronic acid.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	2002			Interchim Intermedia	
Boehringer Ingelheim Ph	2002			WO 02083642 A1	HCAPLUS
Kotobuki Seiyaku Co Ltd	1999			JP 11236369 A	HCAPLUS
Kuragano, T	2002			WO 0238550 A1	HCAPLUS
Rizzi, J	1996			WO 9627583 A	HCAPLUS

L18 ANSWER 4 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2004:1127310 HCAPLUS Full-text
DOCUMENT NUMBER: 142:74355
TITLE: Preparation of 5-aryl-3-hydroxypentanoates as matrix ***metalloproteinase*** inhibitors
INVENTOR(S): Gaines, Simon; ***Holmes, Ian Peter; Watson, Stephen Paul***
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110974	A1	20041223	WO 2004-EP5966	20040601
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH,				

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GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI,
NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM,
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EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE,
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SN, TD, TG

EP 1654213 A1 20060510 EP 2004-739544 20040601
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR
JP 2006526590 T 20061124 JP 2006-508257 20040601
US 2006160875 A1 20060720 US 2005-559600 20051202
PRIORITY APPLN. INFO.: GB 2003-12654 A 20030603
WO 2004-EP5966 W 20040601

OTHER SOURCE(S): MARPAT 142:74355

AB R4ZQXCR1R1'YCR2R3R3' [I; Q = (substituted) 5-6-membered aryl, heteroaryl; X = O, S, NR5, CR6R7; Y = CHOH, CHSH, NOR8, CNR8, CNOR8; Z = bond, CR10R11, O,S,SO,SO2, NR10, OCR10R11, CR10R11O; ZR4Q = atoms to form a (substituted) fused tricyclic group; R1, R1', R3, R3' = H, alkyl, alkylaryl; R2 = CO2R8, CONR5OR9, NR5COR9; R4 = (substituted) 5-6 membered aryl, heteroaryl; R5 = H, alkyl; R6, R7 = H, alkyl, halo; R8, R9 = H, alkyl; R10, R11 = H, alkyl, alkylaryl], were prepared Thus, 5-biphen-4-yl-3-hydroxypentanoic acid (preparation given), diisopropylamine, and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate were stirred together for 5 min. in DMF; thiazolidine was added followed by stirring for 2 h to give 47% 5-biphen-4-yl-3-hydroxy- 1-thiazolidin-3-ylpentan-1-one. The latter and addnl. I inhibited MMP-12 with IC50 <100 μM.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Barron	1968	11	1139	JOURNAL OF MEDICINAL	HCAPLUS
Forsey, P	1998			WO 9809940 A	HCAPLUS
Michael, O	2002			US 6350885 B1	HCAPLUS
Robertson, L	1984	34	1020	EXPERIENTIA	HCAPLUS

L18 ANSWER 5 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN DUPLICATE 5
ACCESSION NUMBER: 2000:94249 HCAPLUS Full-text
DOCUMENT NUMBER: 132:277044
TITLE: Distinct Contributions of Glycoprotein VI and α2β1 Integrin to the Induction of Platelet Protein Tyrosine Phosphorylation and Aggregation
AUTHOR(S): Kamiguti, Aura S.; Theakston, Robert D. G.; *Watson, Steve P.*; Bon, Cassian; Laing, Gavin D.; Zuzel, Mirko
CORPORATE SOURCE: Department of Haematology, Royal Liverpool Hospital, University of Liverpool, Liverpool, UK
SOURCE: Archives of Biochemistry and Biophysics (2000), 374(2), 356-362
CODEN: ABBIA4; ISSN: 0003-9861
PUBLISHER: Academic Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Platelet activation by collagen depends principally on two receptors, α2β1 integrin (GPIa-IIa) and GPVI. During this activation, the nonreceptor protein tyrosine kinase pp72syk is rapidly phosphorylated, but the precise

contribution of α2β1 integrin and GPVI to signaling for this phosphorylation is not clear. We have recently found that proteolysis of platelet α2β1 integrin by the snake venom *metalloproteinase*, jararhagin, results in inhibition of collagen-induced platelet aggregation and pp72syk phosphorylation. In order to verify whether the treatment of platelets with jararhagin had any effect on GPVI signaling, in this study we stimulated platelets treated with either jararhagin or anti-α2β1 antibody with two GPVI agonists, an antibody to GPVI and convulxin. Platelet shape change and phosphorylation of pp72syk by both GPVI agonists was preserved, as was the structure and function of GPVI shown by 125I-labeled convulxin binding to immunopptd. GPVI from jararhagin-treated platelets. In contrast, defective platelet aggregation in response to GPVI agonists occurred in both jararhagin-treated and α2β1-blocked platelets. This apparent cosignaling role of α2β1 integrin for platelet aggregation suggests the possibility of a topog. association of this integrin with GPVI. We found that both platelet α2β1 integrin and GPVI coimmunopptd. with αIIbβ3 integrin. Since platelet aggregation requires activation of αIIbβ3 integrin, defective aggregation in the absence of α2β1 suggests that this receptor may provide a signaling link between GPVI and αIIbβ3. Our study therefore demonstrates that platelet signaling leading to pp72syk phosphorylation initiated with GPVI engagement by either convulxin or GPVI antibody does not depend on α2β1 integrin. However, αIIbβ3 integrin may, in this model, require functional α2β1 integrin for its activation. (c) 2000 Academic Press.

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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Arai, M	1995	89	124	Br J Haematol	MEDLINE
Asazuma, N	1996	75	648	Thromb Haemostasis	HCAPLUS
Berditchevski, F	1995	270	17784	J Biol Chem	HCAPLUS
Clark, E	1994	269	28859	J Biol Chem	HCAPLUS
Clemetson, J	1999	274	29019	J Biol Chem	HCAPLUS
De Luca, M	1995	206	570	Biochem Biophys Res	HCAPLUS
Francischetti, I	1998	353	239	Arch Biochem Biophys	HCAPLUS
Fujii, C	1994	226	243	Eur J Biochem	HCAPLUS
Gao, J	1997	16	6414	Embo J	HCAPLUS
Gibbins, J	1996	271	18095	J Biol Chem	HCAPLUS
Handa, M	1995	73	521	Thromb Haemostasis	HCAPLUS
Ichinobe, T	1995	270	28029	J Biol Chem	
Inoue, T	1997	272	63	J Biol Chem	
Jandrot-Perrus, M	1997	272	27035	J Biol Chem	HCAPLUS
Kamiguti, A	1996	320	635	Biochem J	HCAPLUS
Kamiguti, A	1997	1335	209	Biochim Biophys Acta	
Kamiguti, A	1998	31	853	Braz J Biol Med Res	HCAPLUS
Kamiguti, A	1997	272	32599	J Biol Chem	HCAPLUS
Keely, P	1996	271	26668	J Biol Chem	HCAPLUS
Kehrel, B	1988	71	1074	Blood	HCAPLUS
Kunicki, T	1988	263	4516	J Biol Chem	HCAPLUS
Laemmli, U	1970	227	680	Nature	HCAPLUS
Moroi, M	1989	84	1440	J Clin Invest	MEDLINE
Nieuwenhuis, H	1985	318	470	Nature	HCAPLUS
Paine, M	1992	267	22869	J Biol Chem	HCAPLUS
Petty, H	1996	17	209	Immunol Today	HCAPLUS
Polgar, J	1997	272	13576	J Biol Chem	HCAPLUS
Prado-Franceschi, J	1981	19	875	Toxicon	HCAPLUS
Rubinstein, E	1994	24	3005	Eur J Immunol	HCAPLUS
Saelman, E	1994	83	1244	Blood	HCAPLUS
Santoro, S	1986	46	913	Cell	HCAPLUS

Santoro, S	1995	74	813	Thromb Haemostasis	HCAPLUS
Savage, B	1998	94	657	Cell	HCAPLUS
Slupsky, J	1997	244	168	Eur J Biochem	HCAPLUS
Sugiyama, T	1987	69	1712	Blood	HCAPLUS
Takada, Y	1989	111	709	J Cell Biol	
Timmons, S	1989	169	11	Methods Enzymol	HCAPLUS
Tsuji, M	1997	272	23528	J Biol Chem	HCAPLUS
Vargaftig, B	1983	92	57	Eur J Pharmacol	HCAPLUS

L18 ANSWER 6 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:458564 HCAPLUS Full-text
DOCUMENT NUMBER: 145:139950
TITLE: Isolation and characterization of cotiaractivase, a novel low molecular weight prothrombin activator from the venom of Bothrops cotiara
AUTHOR(S): Senis, Yotis A.; Kim, Paul Y.; Fuller, Gemma L. J.; Garcia, Angel; Prabhakar, Sripadi; Wilkinson, Mark C.; Brittan, Helen; Zitzmann, Nicole; Wait, Robin; Warrell, David A.; ***Watson, Steve P.***; Kamiguti, Aura S.; Theakston, R. David G.; Nesheim, Michael E.; Laing, Gavin D.
CORPORATE SOURCE: Centre for Cardiovascular Sciences, Institute of Biomedical Research, University of Birmingham, Edgbaston, rmingham, B15 2TT, UK
SOURCE: Biochimica et Biophysica Acta, Proteins and Proteomics (2006), 1764(5), 863-871
CODEN: BBAPBW; ISSN: 1570-9639
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, we isolated a novel prothrombin activator from the venom of Bothrops cotiara, a Brazilian lance-headed pit viper (Cotiara, Jararaca preta, Biocotiara), which we have designated "cotiaractivase" (prefix: cotiar- from B. cotiara; suffix: -activase, from prothrombin activating activity). Cotiaractivase was purified using a phenyl-Superose hydrophobic interaction column followed by a Mono-Q anion exchange column. It is a single-chain polypeptide with a mol. weight of 22,931 Da as measured by mass spectroscopy. Cotiaractivase generated active α-thrombin from purified human prothrombin in a Ca2+-dependent manner as assessed by S2238 chromogenic substrate assay and SDS-PAGE. Cotiaractivase cleaved prothrombin at positions Arg271-Thr272 and Arg320-Ile321, which are also cleaved by factor Xa. However, the rate of thrombin generation by cotiaractivase was approx. 60-fold less than factor Xa alone and 17 + 106-fold less than the prothrombinase complex. The enzymic activity of cotiaractivase was inhibited by the chelating agent EDTA, whereas the serine protease inhibitor PMSF had no effect on its activity, suggesting that it is a ***metalloproteinase***. Interestingly, S2238 inhibited cotiaractivase activity non-competitively, suggesting that this toxin contains an exosite that allows it to bind prothrombin independently of its active site. Tandem mass spectrometry and N-terminal sequencing of purified cotiaractivase identified peptides that were identical to regions of the cysteine-rich and disintegrin-like domains of known snake venom ***metalloproteinases***. Cotiaractivase is a unique low mol. weight snake venom prothrombin activator that likely belongs to the ***metalloproteinase*** family of proteins.
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Andrews, R	2001	31	155	Haemostasis	HCAPLUS
Bajzar, L	1990	265	16948	J Biol Chem	HCAPLUS
Brufatto, N	2003	278	6755	J Biol Chem	HCAPLUS

Castro, H	1999	37	1403	Toxicon	HCAPLUS
Fox, J	2005	45	969	Toxicon	HCAPLUS
Francischetti, I	1998	119	21	Comp Biochem Physiol	MEDLINE
Garcia, A	2004	103	2088	Blood	HCAPLUS
Gutierrez, J	2000	82	841	Biochimie	HCAPLUS
Jenny, N	2001		171	Hemostasis and throm	
Kalafatis, M	2005	12	141	Curr Opin Hematol	HCAPLUS
Krishnaswamy, S	1997	36	12080	Biochemistry	HCAPLUS
Lewis, R	2004	24	175	Semin Neurol	
Licklider, L	2002	74	3076	Anal Chem	HCAPLUS
Lu, Q	2005	3	1791	J Thromb Haemost	HCAPLUS
Mann, K	2003	1	1504	J Thromb Haemost	HCAPLUS
Mann, K	1981	80	286	Methods Enzymol	
Nahas, L	1979	41	314	Thromb Haemost	HCAPLUS
Nishida, S	1995	34	1771	Biochemistry	HCAPLUS
Paine, M	1992	267	22869	J Biol Chem	HCAPLUS
Senis, Y	2005	16	191	Platelets	HCAPLUS
Silva, M	2003	369	129	Biochem J	HCAPLUS
Teixeira de, F	2005	100	181	Mem Inst Oswaldo Cru	
Walsh, P	2004	30	461	Semin Thromb Hemost	HCAPLUS
Wijeyewickrema, L	2005	45	1051	Toxicon	HCAPLUS
Zhou, Q	1995	307	411	Biochem J	

L18 ANSWER 7 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:734851 HCAPLUS Full-text
DOCUMENT NUMBER: 141:203977
TITLE: Matrix ***metalloproteinase*** expression and activity in human airway smooth muscle cells
AUTHOR(S): Elshaw, Shona R.; Henderson, Neil; Knox, Alan J.; ***Watson, Susan A.***; Buttle, David J.; Johnson, Simon R.
CORPORATE SOURCE: Division of Therapeutics and Molecular Medicine, University Hospital, Queens Medical Centre, University of Nottingham, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Pharmacology (***2004***), 142(8), 1318-1324
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Airway remodeling is a feature of chronic asthma comprising smooth muscle hypertrophy and deposition of extracellular matrix (ECM) proteins. Matrix ***metalloproteinases*** (MMPs) breakdown ECM, are involved in tissue remodeling and have been implicated in airway remodeling. Although mesenchymal cells are an important source of MMPs, little data are available on airway smooth muscle (ASM) derived MMPs. We therefore investigated MMP and tissue ***inhibitor*** of ***metalloproteinase*** (TIMP) production and activity in human ASM cells. MMPs and TIMPs were examined using quant. real-time RT-PCR, Western blotting, zymog. and a quench fluorescence (QF) assay of total MMP activity. The most abundant MMPs were pro-MMP-2, pro- MMP-3, active MMP-3 and MT1-MMP. TIMP-1 and TIMP-2 expression was low in cell lysates but high in conditioned medium. High TIMP secretion was confirmed by the ability of ASM-conditioned medium to ***inhibit*** recombinant MMP-2 in a QF assay. Thrombin increased MMP activity by activation of pro-MMP-2 independent of the conventional smooth muscle thrombin receptors PAR 1 and 4. In conclusion, ASM cells express pro-MMP-2, pro and active MMP-3, MMP-9 and MT1-MMP. Unstimulated cells secrete excess TIMP 1 and 2, preventing proteolytic activity. MMP-2 can be activated by thrombin which may contribute to airway remodeling.
RETABLE

Referenced Author	Year	VOL	PG	Referenced Work	Referenced

(RAU)	(RPY)	(RVL)	(RPG)	(RWK)	File
Andrade-Gordon, P	1999	96	12257	Proc Natl Acad Sci U	HCAPLUS
Butler, G	1998	273	871	J Biol Chem	HCAPLUS
Chambers, L	2003	285	L619	Am J Physiol	HCAPLUS
Dahlen, B	1999	54	590	Thorax	MEDLINE
Dunsmore, S	1998	102	1321	J Clin Invest	HCAPLUS
Foda, H	1999	277	L174	Am J Physiol	HCAPLUS
Freyer, A	2001	25	569	Am J Respir Cell Mol	HCAPLUS
Gabazza, E	1999	177	253	Lung	HCAPLUS
Hauck, R	1999	277	L22	Am J Physiol	HCAPLUS
Hirst, S	2000	23	335	Am J Respir Cell Mol	HCAPLUS
Hirst, S	1996	9	808	Eur Resp J	HCAPLUS
Hollenberg, M	1999	20	271	Trends Pharm Sci	HCAPLUS
Imai, K	1997	322	809	Biochem J	HCAPLUS
Jeffery, P	2000	94	S9	Respir Med	
Johnson, P	2000	162	2145	Am J Respir Crit Car	MEDLINE
Johnson, S	1999	277	L1109	Am J Physiol	HCAPLUS
Johnson, S	1997	18	288	Trends Pharmacol Sci	HCAPLUS
Knight, C	1992	296	263	FEBS Lett	HCAPLUS
Knight, D	2001	108	797	J All Clin Immunol	HCAPLUS
Lafleur, M	2001	357	107	Biochem J	HCAPLUS
Lemjabbar, H	1999	20	903	Am J Respir Cell Mol	HCAPLUS
MacFarlane, S	2001	53	245	Pharmacol Rev	HCAPLUS
Mautino, G	1999	160	324	Am J Respir Crit Car	MEDLINE
Nagase, H	1999	274	21491	J Biol Chem	HCAPLUS
Nystedt, S	1994	91	9208	Proc Natl Acad Sci U	HCAPLUS
Panettieri, J	1995	13	205	Am J Respir Cell Mol	
Pang, L	1998	161	2509	J Immunol	HCAPLUS
Rawlings, N	1990	6	118	Comput Appl Biosci	HCAPLUS
Sower, L	1999	247	422	Exp Cell Res	HCAPLUS
Terada, M	2004	169	373	Am J Respir Crit Car	
Tran, T	2003	138	865	Br J Pharmacol	HCAPLUS
Whitelock, J	1996	271	10079	J Biol Chem	HCAPLUS

L18 ANSWER 8 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:303578 HCAPLUS Full-text
DOCUMENT NUMBER: 139:20519
TITLE: Expression and regulation of tissue *inhibitor* of *metalloproteinase*-1 and matrix *metalloproteinases* by intestinal myofibroblasts in inflammatory bowel disease
AUTHOR(S): McKaig, Brian C.; McWilliams, Daniel; *Watson, Sue A.*; Mahida, Yashwant R.
CORPORATE SOURCE: Division of Gastroenterology, University Hospital, Queen's Medical Centre, Nottingham, UK
SOURCE: American Journal of Pathology (*2003*), 162(4), 1355-1360
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Intestinal fibrosis and strictures frequently occur in Crohn's disease but not ulcerative colitis. We have recently shown that, compared to myofibroblasts obtained from normal and ulcerative colitis tissue, myofibroblasts isolated from fibrotic Crohn's disease mucosal samples express significantly lower amts. of transforming growth factor (TGF)-β3, but the expression of TGF-β2 was significantly greater. We now report that in myofibroblast cultures established from fibrotic Crohn's disease mucosal samples there is significantly higher constitutive expression of tissue *inhibitor* of

metalloproteinase (TIMP)-1 compared to similar cells isolated from normal or ulcerative colitis tissue. Myofibroblasts derived from normal mucosa and from mucosa affected by ulcerative colitis or Crohn's disease also expressed matrix *metalloproteinase* (MMP)-1, MMP-2, and MMP-3 but did not express MMP-9. Recombinant (r) TGF-β1 and rTGF-β2, but not rTGF-β3, induced expression of TIMP-1 in normal intestinal myofibroblasts. These studies illustrate a potential mechanism by which differential expression of isoforms of TGF-β may lead to excessive deposition of extracellular matrix and stricture formation via TIMP-1-mediated *inhibition* of MMP activity.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bailey, C	1994	47	113	J Clin Pathol	MEDLINE
Baugh, M	1999	117	814	Gastroenterology	HCAPLUS
Border, W	1994	331	1286	N Engl J Med	HCAPLUS
Brew, K	2000	1477	267	Biochim Biophys Acta	HCAPLUS
Gomez, D	1997	74	111	Eur J Cell Biol	HCAPLUS
Graham, M	1995	1	220	Inflamm Bowel Dis	
Graham, M	1995	1	220	Inflamm Bowel Dis	
Heuschkel, R	2000	47	57	Gut	HCAPLUS
Ichiki, Y	1995	104	124	J Invest Dermatol	HCAPLUS
Mahida, Y	1997	273	G1341	Am J Physiol	HCAPLUS
McAlindon, M	1998	115	841	Gastroenterology	MEDLINE
McKaig, B	1999	276	G1087	Am J Physiol	HCAPLUS
McKaig, B	2002	282	C172	Am J Physiol	HCAPLUS
Moore, R	1989	257	G274	Am J Physiol	MEDLINE
Nagase, H	1999	274	21491	J Biol Chem	HCAPLUS
Overall, C	1991	266	14064	J Biol Chem	HCAPLUS
Pender, S	1997	158	1582	J Immunol	HCAPLUS
Plateroti, M	1998	274	G945	Am J Physiol	HCAPLUS
Powell, D	1999	277	C1	Am J Physiol	HCAPLUS
Powell, D	1999	277	C183	Am J Physiol	HCAPLUS
Salmela, M	2002	51	540	Gut	HCAPLUS
Shah, M	1994	107	1137	J Cell Sci	HCAPLUS
Shah, M	1995	108	985	J Cell Sci	HCAPLUS
Vaalamo, M	1998	152	1005	Am J Pathol	HCAPLUS
van Tol, E	1999	277	G245	Am J Physiol	HCAPLUS
Von Lampe, B	2000	47	63	Gut	HCAPLUS

L18 ANSWER 9 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:152302 HCAPLUS Full-text
DOCUMENT NUMBER: 137:275075
TITLE: Effect of preoperative radiotherapy on matrilysin gene expression in rectal cancer
AUTHOR(S): Kumar, A.; Collins, H.; Van Tam, J.; Scholefield, J. H.; *Watson, S. A.*
CORPORATE SOURCE: Section of Surgery, University Hospital, Academic Unit of Cancer Studies, Nottingham, NG7 2UH, UK
SOURCE: European Journal of Cancer (*2002*), 38(4), 505-510
CODEN: EJCAEL; ISSN: 0959-8049
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Matrilysin, a member of matrix *metalloproteinase* family, is believed to play a significant role in the growth and proliferation of colon cancer cells. Overexpression of the matrilysin gene has been shown to correlate with Dukes' stage and increased metastatic potential in colorectal cancer. The aim of this study was to evaluate the effect of preoperative high-dose radiotherapy

(25 Gy in five fractions over 5 days) on matrilysin (MMP-7) gene expression, in patients with resectable rectal cancer, by a quant. reverse transcriptase-polymerase chain reaction (RT-PCR). Biopsy samples of tumor (n=30) and distant normal mucosa (n=12) from 15 patients were obtained pre- and post-radiotherapy. Messenger (m)RNA was extracted from all of the tissue samples and reverse transcribed to double-stranded cDNA. Quant. RT-PCR was performed to study the effect of preoperative radiotherapy on matrilysin gene expression in both the tumor and normal mucosal specimens. Matrilysin mRNA values were expressed relative to glyceraldehyde-3-phosphate dehydrogenase (GAPDH) for each sample. In 14 out of 15 cases, matrilysin mRNA was detected in the cancerous tissue. Although all six normal mucosal specimens expressed matrilysin mRNA, the levels were approx. 10-fold lower compared with those seen in the paired tumor samples. Preoperative radiotherapy led to a significant 6- to 7-fold increase (P=0.001) in the expression of matrilysin mRNA in rectal cancer tissue. In contrast, there was no significant change in the matrilysin mRNA expression of normal mucosal specimens post-radiotherapy. Preoperative high-dose radiotherapy upregulates matrilysin gene expression in rectal cancer. Matrilysin ***inhibition*** may be a useful preventive or therapeutic adjunct to radiotherapy in rectal cancer.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Adachi, Y		45	252	Gut	HCAPLUS
Anon	1997	336	980	N Engl J Med	
Babu, J	1993	165	207	J Immunol Methods	HCAPLUS
Becker-Andre, M	1989	17	9437	Nucliec Acids Res	HCAPLUS
Boag, A	1994	144	585	Am J Path	HCAPLUS
Cedermark, B	1995	75	2269	Cancer	MEDLINE
Chamber, A	1997	89	1260	J Natl Cancer Inst	
Clements, J	1997	74	85	J Neuroimmunol	HCAPLUS
Crabbe, T	1994	345	14	FEBS Lett	HCAPLUS
Davies, B	1993	53	5365	Cancer Res	HCAPLUS
Declerck, Y	1992	52	701	Cancer Res	HCAPLUS
Gaire, M	1994	269	2032	J Biol Chem	HCAPLUS
Gilliland, G	1990	87	2725	Proc Natl Acad Sci U	HCAPLUS
Gridley, D	1998	22	20	Canc Detect Prev	HCAPLUS
Ingber, D	1990	87	3579	Proc Natl Acad Sci U	HCAPLUS
Ishikawa, T	1996	107	5	Cancer Lett	HCAPLUS
Johnson, M	1994	160	194	J Cell Physiol	HCAPLUS
Khokha, R	1992	10	365	Clin Exp Metastasis	HCAPLUS
Kumar, A	2000	84	960	Br J Cancer	
Kumar, A	1999	44	91	Gut	
Marsh, P	1994	37	1205	Dis Colon Rectum	MEDLINE
Mauviel, A	1993	53	288	J Cell Biochem	HCAPLUS
McDonnell, S	1991	4	527	Mol Carcinog	HCAPLUS
McDonnell, S	1990	10	4284	Mol Cell Biol	HCAPLUS
Miyazaki, K	1990	50	7758	Cancer Res	HCAPLUS
Mori, M	1995	75	1516	Cancer	MEDLINE
Muller, D	1993	53	165	Cancer Res	HCAPLUS
Murphy, G	1991	277	277	Biochem J	HCAPLUS
Newell, K	1994	10	199	Mol Carcinog	MEDLINE
Rodgers, W	1993	168	253	Am J Obstet Gynecol	HCAPLUS
Sawaya, R	1994	56	214	Int J Cancer	HCAPLUS
Sheela, S	1986	7	201	Carcinogenesis	HCAPLUS
Simmonds, P	1990	64	864	J Virol	MEDLINE
Tsuchiya, Y	1993	53	1397	Cancer Res	HCAPLUS
Vu, T	1998	93	411	Cell	HCAPLUS
Welch, D	1990	87	7678	Proc Nat Acad Sci (W	HCAPLUS
Wells, G	1996	18	332	Glia	MEDLINE

Wilson, C	1996	28	123	Int J Biochem Cell B	HCAPLUS
Wilson, C	1997	94	1402	Proc Natl Acad Sci U	HCAPLUS
Witty, J	1994	54	4805	Cancer Res	HCAPLUS
Woessner, J	1988	263	16918	J Biol Chem	HCAPLUS
Yashimoto, M	1993	54	614	Int J Cancer	

L18 ANSWER 10 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:560817 HCAPLUS Full-text
DOCUMENT NUMBER: 136:65499
TITLE: A novel viper venom ***metalloproteinase***, alborhagin, is an agonist at the platelet collagen receptor GPVI
AUTHOR(S): Andrews, Robert K.; Gardiner, Elizabeth E.; Asazuma, Naoki; Berlanga, Oscar; Tulasne, David; Nieswandt, Bernhard; Smith, A. Ian; Berndt, Michael C.; ***Watson, Stephen P.***
CORPORATE SOURCE: Hazel and Pip Appel Vascular Biology Laboratory, Baker Medical Research Institute, Melbourne, 8008, Australia
SOURCE: Journal of Biological Chemistry (*2001*), 276(30), 28092-28097
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The interaction of platelet membrane glycoprotein VI (GPVI) with collagen can initiate (patho)physiol. thrombus formation. The viper venom C-type lectin family proteins convulxin and alboaggregin-A activate platelets by interacting with GPVI. In this study, the authors isolated from white-lipped tree viper (Trimeresurus albolabris) venom, alborhagin, which is functionally related to convulxin because it activates platelets but is structurally different and related to venom ***metalloproteinases***. Alborhagin-induced platelet aggregation (EC50, <7.5 μg/mL) was ***inhibitable*** by an anti-αIIbβ3 antibody, CRC64, and the Src family kinase ***inhibitor*** PP1, suggesting that alborhagin activates platelets, leading to αIIbβ3-dependent aggregation. Addnl. evidence suggested that, like convulxin, alborhagin activated platelets by a mechanism involving GPVI. First, alborhagin- and convulxin-treated platelets showed a similar tyrosine phosphorylation pattern, including a similar level of phospholipase Cγ2 phosphorylation. Second, alborhagin induced GPVI-dependent responses in GPVI-transfected K562 and Jurkat cells. Third, alborhagin-dependent aggregation of mouse platelets was ***inhibited*** by the anti-GPVI monoclonal antibody JAQ1. Alborhagin had minimal effect on convulxin binding to GPVI-expressing cells, indicating that these venom proteins may recognize distinct binding sites. Characterization of alborhagin as a GPVI agonist that is structurally distinct from convulxin demonstrates the versatility of snake venom toxins and provides a novel probe for GPVI-dependent platelet activation.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Andrews, R	1989	28	8317	Biochemistry	HCAPLUS
Andrews, R	1996	35	12629	Biochemistry	HCAPLUS
Andrews, R	1997	29	91	Int J Biochem Cell B	HCAPLUS
Andrews, R	2000	38	775	Toxicon	HCAPLUS
Asazuma, N	2001	97	3989	Blood	HCAPLUS
Asazuma, N	2000	275	33427	J Biol Chem	HCAPLUS
Berlanga, O	2000	96	2740	Blood	HCAPLUS
Berndt, M	1985	151	637	Eur J Biochem	HCAPLUS

Briddon, S	1999	337	203	Biochem J	
De Luca, M	1995	206	570	Biochem Biophys Res	HCAPLUS
De Luca, M	1995	270	26734	J Biol Chem	HCAPLUS
Dormann, D	2001	97	2333	Blood	
Ezumi, Y	1998	188	267	J Exp Med	HCAPLUS
Falati, S	1999	94	1648	Blood	HCAPLUS
Fujimura, Y	1991	30	1957	Biochemistry	HCAPLUS
Hers, I	2000	267	2088	Eur J Biochem	HCAPLUS
Ichinohe, T	1997	272	63	J Biol Chem	HCAPLUS
Jandrot-Perrus, M	1997	272	27035	J Biol Chem	HCAPLUS
Jeon, O	1999	263	526	Eur J Biochem	HCAPLUS
Khaspekova, S	1993	85	332	Br J Haematol	HCAPLUS
Kini, R	1992	30	265	Toxicon	HCAPLUS
Kini, R	1996	34	1287	Toxicon	HCAPLUS
Kowalska, M	1998	79	609	Thromb Haemostasis	HCAPLUS
Kroll, M	1993	268	3520	J Biol Chem	HCAPLUS
Kulkarni, S	2000	105	783	J Clin Invest	HCAPLUS
Leduc, M	1998	333	389	Biochem J	HCAPLUS
Navdaev, A	2001	276	20882	J Biol Chem	HCAPLUS
Nieswandt, B	2000	275	23998	J Biol Chem	HCAPLUS
Nieswandt, B	2001	193	459	J Exp Med	HCAPLUS
Paine, M	1992	267	22869	J Biol Chem	HCAPLUS
Pasquet, J	1999	342	171	Biochem J	HCAPLUS
Peng, M	1992	67	702	Thromb Haemostasis	HCAPLUS
Polgar, J	1997	272	13576	J Biol Chem	HCAPLUS
Savage, B	1996	84	289	Cell	HCAPLUS
Scholey, J	1980	287	233	Nature	HCAPLUS
Schulte, V	2001	276	364	J Biol Chem	HCAPLUS
Takeya, H	1990	265	16068	J Biol Chem	HCAPLUS
Ward, C	1996	35	4929	Biochemistry	HCAPLUS
Ward, C	1996	34	1203	Toxicon	HCAPLUS
Watson, S	1999	82	365	Thromb Haemostasis	HCAPLUS
Weiss, H	1995	74	117	Thromb Haemostasis	HCAPLUS

L18 ANSWER 11 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:527262 HCAPLUS Full-text
DOCUMENT NUMBER: 136:67891
TITLE: Spectrum of matrix *metalloproteinase* expression in primary and metastatic colon cancer: Relationship to the tissue *inhibitors* of *metalloproteinases* and membrane type-1-matrix *metalloproteinase*
AUTHOR(S): Collins, H. M.; Morris, T. M.; *Watson, S. A.*
CORPORATE SOURCE: The Academic Unit of Cancer Studies, Division of Gl Surgery, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer (*2001*), 84(12), 1664-1670
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The matrix *metalloproteinases*, MMP-2 are MMP-9, are capable of degrading components of the basement membrane, a vital barrier breached during the progression of colorectal cancer. The regulation of MMP-2 activation and subsequent targets is vital to understanding the metastatic process. MMP-2 was not expressed by colorectal cancer cells (C170 and C170HM2) in vitro but by stromal fibroblasts (46BR.1Gl). There was induction of this MMP upon transwell co-cultivation of the colon cancer cells with the fibroblasts but in vivo growth did not lead to a similar increase in the metastatic tumor cells (C170HM2), MMP-2 again being attributed to the stromal cells. MMP-2 mRNA was

overexpressed in human colorectal tumors compared to normal colorectal tissue, which correlated with Dukes' stage and immunolocalized to the stromal compartment of the tumor tissue. The active form of the MMP-2 enzyme was also present in the colorectal tumor tissue (7/8) but essentially absent in all normal colon samples examined (1/8). MMP-2 activation was not related to an increase in MT-1-MMP mRNA or a decrease in the specific *inhibitor* TIMP-2 in human tissue. There was however an increase in MMP-2/TIMP-2 ratio in tumor compared to normal, MMP-9, a target of active MMP-2, was present in the metastatic cell line but expression was down-regulated in the tumor cells in vivo, gelatin anal. revealed that MMP-9 was almost entirely attributable to the murine host, confirmed by PCR. There was no increase in mRNA for MMP-9 or its specific *inhibitor* TIMP-1 in colorectal tumor tissue compared to normal, MMP-9 protein localized to the inflammatory infiltrate. Fibroblast cells may provide malignant epithelial cells with a ready source of enzyme which is crucial to the metastatic process.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Birkedal-Hanson, H	1993	4	197	Crit Rev Oral Biol M	
Biswas, C	1995	55	434	Cancer Res	HCAPLUS
Brown, P	1990	50	6184	Cancer Res	HCAPLUS
Davies, B	1993	53	5365	Cancer Res	HCAPLUS
Durrant, L	1986	53	37	Br J Cancer	MEDLINE
D'Errico, A	1991	4	239	Mod Pathol	MEDLINE
Ellerbroek, S	1999	59	1635	Cancer Res	HCAPLUS
Fridman, R	1995	55	2548	Cancer Res	HCAPLUS
Harris, E	1990	322	1277	New Engl J Med	
Heppner, K	1996	149	273	Am J Pathol	MEDLINE
Hewitt, R	1991	49	666	Int J Cancer	HCAPLUS
Hyuga, S	1994	54	3611	Cancer Res	HCAPLUS
Lehti, K	1998	334	345	Biochem J	HCAPLUS
Lengyel, E	1995	55	963	Cancer Res	HCAPLUS
Liabakk, N	1996	56	190	Cancer Res	HCAPLUS
Masuda, H	1999	42	393	Dis Colon Rectum	MEDLINE
Masure, S	1993	218	129	Eur J Biochem	HCAPLUS
McDonnell, S	1999	17	341	Clin Exp Metas	MEDLINE
Noel, A	1994	56	331	Int J Cancer	HCAPLUS
Ornstein, D	1999	17	202	Clin Exp Metas	
Page, R	1991	26	230	J Periodont Res	MEDLINE
Parsons, S	1998	78	1495	Br J Cancer	HCAPLUS
Pender, S	1997	158	1582	J Immunol	HCAPLUS
Polette, M	1997	15	157	Clin Exp Metas	MEDLINE
Poulsom, R	1992	141	389	Am J Pathol	MEDLINE
Pyke, C	1993	142	359	Am J Pathol	HCAPLUS
Saito, K	2000	86	24	Int J Cancer	MEDLINE
Sato, H	1994	370	61	Nature	HCAPLUS
Segain, J	1996	56	5506	Cancer Res	HCAPLUS
Shimizu, S	1996	56	3366	Cancer Res	HCAPLUS
Stanton, H	1998	111	2789	J Cell Sci	HCAPLUS
Stetler-Stevenson, W	1993	7	1434	FASEB J	HCAPLUS
Watson, S	1993	29	1740	Eur J Cancer	
Wells, G	1996	18	332	Glia	MEDLINE
Westermarck, J	1999	13	781	FASEB J	HCAPLUS
Zeng, Z	1995	72	575	Br J Cancer	HCAPLUS

L18 ANSWER 12 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:168274 HCAPLUS Full-text
DOCUMENT NUMBER: 133:70806
TITLE: Increased type-IV collagenase (MMP-2 and MMP-9)

activity following preoperative radiotherapy in rectal cancer

AUTHOR(S): Kumar, A.; Collins, H. M.; Scholefield, J. H.; ***Watson, S. A.***

CORPORATE SOURCE: Academic Unit of Cancer Studies, University Hospital, Nottingham, NG7 2UH, UK

SOURCE: British Journal of Cancer (*2000*), 82(4), 960-965
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The aim of this study was to investigate the effect of preoperative high-dose radiotherapy (25 Gy in 5 fractions over 5 days) on the type-IV collagenase protein profile, in patients with resectable rectal cancer, by gelatin zymog. Biopsy samples of tumor and distant normal mucosa from 12 patients with resectable rectal cancer were obtained pre- and post-radiotherapy. Expression of type-IV collagenases (both pro- and active forms) was studied using gelatin zymog. Enzyme levels were normalized for total protein content of each sample. Rectal cancer specimens expressed both pro (72 kDa) and active (62 kDa) forms of MMP-2 but only the pro form of MMP-9 (92 kDa). Normal mucosa showed expression of the pro forms of MMP-2 and MMP-9 while no active form of either enzyme was detected in any of the samples. A significant three- to fourfold increase ($P < 0.01$) of active matrix ***metalloproteinases*** (MMP)-2 (62 kDa) was seen in malignant rectal mucosa after radiotherapy. The effect of radiotherapy also led to a twofold increase ($P = 0.047$) of pro MMP-2 (72 kDa) and a two- to threefold increase ($P = 0.03$) of the precursor form of MMP-9 (92 kDa). In contrast, in normal mucosa expression of the precursor form of MMP-9 (92 kDa) did not change after radiation, and no significant effect on the levels of pro MMP-2 (72 kDa) was observed Preoperative high-dose radiotherapy leads to an increase in activity of type-IV collagenases in patients with resectable rectal cancer. Type-IV collagenase ***inhibition*** may be a useful therapeutic adjunct to radiotherapy in rectal cancer.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Abulafi, A	1994	81	7	Br J Surg	MEDLINE
Adam, I	1994	344	707	Lancet	MEDLINE
Albini, A	1994	8	1237	AIDS	HCAPLUS
Azzam, H	1993	85	1758	J Natl Cancer Inst	HCAPLUS
Ballin, M	1988	154	832	Biochem Biophys Res	HCAPLUS
Boag, A	1994	144	585	Am J Path	HCAPLUS
Brown, P	1993	11	183	Clin Exp Metastasis	MEDLINE
Cedermark, B	1995	75	2269	Cancer	MEDLINE
Chambers, A	1997	89	1260	J Natl Cancer Inst	HCAPLUS
Chandler, S	1995	201	223	Neurosci Lett	HCAPLUS
Davies, B	1993	67	1126	Br J Cancer	MEDLINE
Davies, B	1993	53	5365	Cancer Res	HCAPLUS
Duffy, M	1998	12	1343	Int J Oncol	HCAPLUS
Heussen, C	1980	102	196	Anal Biochem	HCAPLUS
Jaziorka, M	1994	9	141	Int J Colorectal Dis	
Johnson, M	1994	160	194	J Cell Phys	HCAPLUS
Kinoshita, T	1996	56	2535	Cancer Res	HCAPLUS
Kleiner, D	1994	218	325	Anal Biochem	HCAPLUS
Liabakk, N	1996	56	190	Cancer Res	HCAPLUS
Marsh, P	1994	37	1205	Dis Colon Rectum	MEDLINE
Meyers, M	1989	39	21	CA Cancer J Clin	
Moll, U	1990	50	6162	Cancer Res	HCAPLUS
Moriya, Y	1989	32	307	Dis Colon Rectum	MEDLINE

Muller, D	1993	53	165	Cancer Res	HCAPLUS
Murphy, G	1992	7	120	Am J Resp Cell Mol B	HCAPLUS
Nakajima, M	1990	82	1890	J Natl Cancer Inst	HCAPLUS
Parsons, S	1998	78	1495	Br J Cancer	HCAPLUS
Poulsom, R	1992	141	389	Am J Pathol	MEDLINE
Pyke, C	1993	142	359	Am J Pathol	HCAPLUS
Quirke, P	1986	ii	996	Lancet	
Sawaya, R	1994	56	214	Int J Cancer	HCAPLUS
Seir, C	1996	74	413	Br J Cancer	
Sheela, S	1986	7	201	Carcinogenesis	HCAPLUS
Stetler-Stevenson, W	1993	7	1434	FASEB J	HCAPLUS
Strongin, A	1995	270	5331	J Biol Chem	HCAPLUS
Swedish Rectal Cancer T	1997	336	980	N Engl J Med	
Takahashi, K	1994	93	2357	J Clin Invest	MEDLINE
Tomita, T	1996	39	1255	Dis Colon Rectum	MEDLINE
Turpeenniemi-Hujanen, T	1985	75	99	J Natl Cancer Inst	HCAPLUS
Urbanski, S	1993	2	81	Diag Mol Pathol	MEDLINE
Vu, T	1998	93	411	Cell	HCAPLUS
Yamagata, S	1988	151	158	Biochem Biophys Res	HCAPLUS
Yamagata, S	1991	59	51	Cancer Lett	MEDLINE
Zeng, Z	1995	72	575	Br J Cancer	HCAPLUS
Zeng, Z	1996	14	3133	J Clin Oncol	MEDLINE
Zucker, S	1993	53	140	Cancer Res	MEDLINE

L18 ANSWER 13 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:629238 HCAPLUS Full-text

DOCUMENT NUMBER: 132:131883

TITLE: Inhibition of tumor growth by marimastat in a human xenograft model of gastric cancer: relationship with levels of circulating CEA

AUTHOR(S): ***Watson, S. A.***; Morris, T. M.; Collins, H. M.; Bawden, L. J.; Hawkins, K.; Bone, E. A.

CORPORATE SOURCE: Cancer Studies Unit, Department of Surgery, Queen's Medical Centre, Nottingham, UK

SOURCE: British Journal of Cancer (*1999*), 81(1), 19-23
CODEN: BJCAAI; ISSN: 0007-0920

PUBLISHER: Churchill Livingstone

DOCUMENT TYPE: Journal

LANGUAGE: English

AB ***Inhibition*** of matrix ***metalloproteinases*** (MMPs) is an attractive approach to adjuvant therapy in the treatment of cancer. Marimastat is the first orally administered, synthetic MMP ***inhibitor*** to be evaluated, in this capacity, in the clinic. Measurement of the rate of change of circulating tumor antigens was used for evaluating biol. activity and defining optimum dosage in the early clin. trials of marimastat. Although tumor antigen levels have been used in the clin. management of cancer for many years, they have not been validated as markers of disease progression. In order to investigate the relationship between the effects of marimastat on tumor growth and circulating tumor antigen levels, mice bearing the human gastric tumor, MGLVA1, were treated with marimastat. The MMP ***inhibitor*** exerted a significant therapeutic effect, reducing tumor growth rate by 48% ($P = 0.0005$), and increasing median survival from 19 to 30 days ($P = 0.0001$). In addition, carcinoembryonic antigen (CEA) levels were measured in serum samples from animals sacrificed at regular intervals, and correlated with excised tumor weight It was shown that the natural log of the CEA concentration was linearly related to the natural log of the tumor weight and that treatment was not a significant factor in this relationship ($P = 0.7$). In conclusion, circulating CEA levels were not directly affected by marimastat, but did reflect tumor size. These results

support the use of cancer antigens as markers of biol. activity in early phase trials of non-cytotoxic anticancer agents.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Allen-Mersh, T	1987	28	1625	Gut	MEDLINE
Anderson, I	1996	56	715	Cancer Res	HCAPLUS
Anon	1981	282	373	Br Med J	
Chirivi, R	1994	58	460	Int J Cancer	HCAPLUS
Cottam, D	1993	2	861	Int J Oncol	HCAPLUS
Davies, B	1993	53	2087	Cancer Res	HCAPLUS
D'Errico, A	1991	4	239	Modern Pathol	MEDLINE
Eccles, S	1996	56	2815	Cancer Res	HCAPLUS
Giavazzi, R	1998	4	985	Clin Cancer Res	HCAPLUS
Goldenberg, D	1981	101	239	J Cancer Res Clin On	HCAPLUS
Gore, M	1996	348	263	Lancet	MEDLINE
Hida, J	1996	39	74	Dis Colon Rectum	MEDLINE
Hine, K	1984	25	682	Gut	MEDLINE
Hojo, J	1977	91	737	Niigata Igakukai Zas	
Honda, M	1996	39	444	Gut	MEDLINE
Kleiner, D	1993	5	891	Curr Opin Cell Biol	HCAPLUS
Liotta, L	1990	1	99	Sem Cancer Biol	MEDLINE
Matrisian, L	1992	14	455	Bioessays	HCAPLUS
McDonnell, S	1991	4	527	Molecular Carcinogen	HCAPLUS
Millar, A	1996	7	123	Ann Oncol	
Millar, A	1996	348	263	Lancet	
Nemunaitis, J	1998	4	1101	Clin Cancer Res	HCAPLUS
Pimm, M	1992	118	367	J Cancer Res and Cli	HCAPLUS
Primrose, J	1999	79	509	Br J Cancer	HCAPLUS
Sledge, G	1995	87	1546	J Natl Cancer Inst	HCAPLUS
Stetler-Stevenson, W	1996	7	147	Semin Cancer Biol	HCAPLUS
Taraboletti, G	1995	87	293	J Natl Cancer Inst	HCAPLUS
Wang, X	1994	54	4726	Cancer Res	HCAPLUS
Ward, U	1993	67	1132	Br J Cancer	MEDLINE
Watson, S	1995	55	3629	Cancer Res	HCAPLUS
Watson, S	1990	45	90	Int J Cancer	HCAPLUS
Watson, S	1991	83	866	J Natl Cancer Inst	MEDLINE

L18 ANSWER 14 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:426328 HCAPLUS Full-text
DOCUMENT NUMBER: 129:197420
TITLE: Matrix *metalloproteinase inhibitors* : a review
AUTHOR(S): *Watson, Susan A.*; Tierney, Gill
CORPORATE SOURCE: Cancer Studies Unit, Department of Surgery, Queens Medical Centre, University of Nottingham, Nottingham, UK
SOURCE: BioDrugs (*1998*), 9(4), 325-335
CODEN: BIDRF4; ISSN: 1173-8804
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 44 refs. The matrix *metalloproteinases* (MMPs) are a family of closely related, zinc-dependent proteolytic enzymes. Collectively, they are capable of degrading all the components of the extracellular matrix and as such are involved in a number of physiol. and pathol. processes. The extracellular matrix is the principal barrier to tumor growth and spread, and there is evidence that MMPs play a role in the processes of tumor growth and metastasis. Therefore, *inhibitors* of MMPs may be of value in the treatment of

malignant disease. There exist naturally occurring *inhibitors* of these enzymes known as "tissue *inhibitors* of MMPs", or TIMPs. Although there have been considerable preclin. studies on these *inhibitors*, they are as yet unavailable for use as therapeutic drugs. Research in this field has focused largely on the development of low mol. weight (<500D) synthetic *inhibitors* of MMPs. In this review we focus on the various subgroups of MMP *inhibitors* now available, their preclin. evaluation and the limited information available from preliminary clin. trials. We comment on the suitability of the preclin. models used and the difficulty in designing clin. trials of these drugs. We focus on future developments which may involve the use of these drugs in combination with existing chemotherapeutic regimens to achieve a synergistic effect.

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anderson, I	1996	56	715	Cancer Res	HCAPLUS
Beattie, G	1994			8th NCI-EORTC Sympos	
Bode, W	1994	13	1263	EMBO J	HCAPLUS
Brown, P	1995	6	967	Ann Oncol	MEDLINE
Chander, S	1995	84	404	J Pharm Sci	HCAPLUS
Chirivi, R	1994	58	460	Int J Cancer	HCAPLUS
Davies, B	1993	53	2087	Cancer Res	HCAPLUS
de Takats, P	1996	73	51	Br J Cancer	
Declerck, Y	1991	51	2151	Cancer Res	HCAPLUS
Declerck, Y	1992	52	701	Cancer Res	HCAPLUS
Eccles, S	1996	56	2815	Cancer Res	HCAPLUS
Galardy, R	1994	54	4715	Cancer Res	HCAPLUS
Golub, L	1991	2	297	Crit Rev Oral Biol M	MEDLINE
Jarvinen, M	1987	82	5	Acta Histochem	HCAPLUS
Johnson, W	1987	2	1	Enzyme Inhibition	HCAPLUS
Karakiulakis, G	1990	1035	218	Biochim Biophys Acta	HCAPLUS
Khokha, R	1992	10	365	Clin Exp Metastasis	HCAPLUS
Khokha, R	1994	86	299	J Natl Cancer Inst	HCAPLUS
Kolber, D	1995	87	304	J Natl Cancer Inst	HCAPLUS
Koop, S	1994	54	4791	Cancer Res	HCAPLUS
Lee, W	1991	26	470	J Periodont Res	
Liu, L	1995	62	345	Int J Cancer	HCAPLUS
Macaulay, V	1995	71	11	Br J Cancer	
Maione, T	1990	237	77	Science	
Mignatti, P	1996	47	487	Cell	
Montgomery, A	1994	54	5467	Cancer Res	HCAPLUS
Naito, K	1994	58	730	Int J Cancer	HCAPLUS
Nicoletti, M	1996	32A	6	Eur J Cancer	
Reich, R	1988	48	3307	Cancer Res	HCAPLUS
Richards, C	1993	150	5596	J Immunol	HCAPLUS
Schultz, R	1988	48	5539	Cancer Res	HCAPLUS
Sharpe, R	1990	82	848	J Natl Cancer Inst	HCAPLUS
Sledge, G	1995	87	293	J Natl Cancer Inst	
Stetler-Stevenson, W	1989	264	17374	J Biol Chem	HCAPLUS
Tamargo, R	1991	51	672	Cancer Res	HCAPLUS
Taraboletti, G	1995	87	293	J Natl Cancer Inst	HCAPLUS
Vincenti, M	1994	37	1115	Arthritis Rheum	MEDLINE
Wang, X	1994	54	4726	Cancer Res	HCAPLUS
Watanabe, M	1996	77	1676	Cancer Suppl	HCAPLUS
Watson, S	1996	74	1354	Br J Cancer	HCAPLUS
Watson, S	1996	73	29	Br J Cancer	
Watson, S	1995	55	3629	Cancer Res	HCAPLUS
Zubair, A	1996	73	42	Br J Cancer	
Zucker, M	1991	198	693	Proc Soc Exp Biol Me	HCAPLUS

L18 ANSWER 15 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:707101 HCAPLUS Full-text
DOCUMENT NUMBER: 126:604
TITLE: Therapeutic effect of the matrix *metalloproteinase inhibitor*, batimastat, in a human colorectal cancer ascites model
AUTHOR(S): *Watson, S. A.*; Morris, T. M.; Parsons, S. L.; Steele, R. J. C.; Brown, P. D.
CORPORATE SOURCE: Cancer Studies Unit, Department Surgery, Queen's Medical Centre, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer (*1996*), 74(9), 1354-1358
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Stockton
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The matrix *metalloproteinase inhibitor* batimastat was administered to a human colorectal cancer ascites model, which was initiated by injection of C170HM2 cells into the peritoneal cavity of SCID mice and resulted in solid tumor deposits and ascites formation. The cell line expressed both the 72 and 92 kDa forms of gelatinase by zymog. Batimastat administered from day 0 (40 mg kg-1) reduced the volume of ascites to 21% of control in mice treated from day 0 but not day 10. Formation of solid peritoneal deposits was significantly reduced to 775 of vehicle control when batimastat was administered from day 0 and 695 of control when administered from day 10. Thus, batimastat has the ability to reduce the volume of ascites forming in SCID mice injected i.p. with the human colorectal cell line, C170HM2, when administered from day 0 but not from day 10. Solid peritoneal tumor deposits were significantly reduced in both treatment groups, highlighting the therapeutic potential of batimastat in this clin. condition.

L18 ANSWER 16 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:755214 HCAPLUS Full-text
DOCUMENT NUMBER: 123:160320
TITLE: *Inhibition* of organ invasion by the matrix *metalloproteinase inhibitor* batimastat (BB-94) in two human colon carcinoma metastasis models
AUTHOR(S): *Watson, Susan A.*; Morris, Teresa M.; Robinson, Graham; Crimmin, Michael J.; Brown, Peter D.; Hardcastle, Jack D.
CORPORATE SOURCE: Cancer Studies Unit., Univ. of Hospital, Nottingham, NG7 2RD, UK
SOURCE: Cancer Research (*1995*), 55(16), 3629-33
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of the matrix *metalloproteinase inhibitor* batimastat was evaluated in two human colorectal cancer metastasis models involving: (a) the liver-invasive tumor C170HM2 and (b) the lung-invasive tumor AP5LV, both of which have been shown to express the Mr 72,000 type IV collagenase. Batimastat at concns. between 0.01 and 3.0 μg/ml had no direct cytotoxic effects on the in vitro growth of the cell lines. In the liver-invasive tumor model, batimastat administered i.p. from day 10 to termination of the therapy (day 39) at 40 mg/kg reduced both the mean number of liver tumors (35% of vehicle-treated control) and the cross-sectional area of the tumors (43% of vehicle-treated control). In the lung-invasive tumor model, batimastat administered daily (40

mg/kg i.p.) significantly reduced tumor weight within the lung (72% of vehicle-treated control) but did not significantly affect nodule number In the latter model, in which the take rate was unaffected, tumor cells were introduced into the lateral tail vein, and lung localization may have been a phys. phenomenon not involving invasion. In the former model, tumor cells were introduced directly into the peritoneal cavity, and from there the cells adhered to and invaded the liver capsule. Because the take rate is significantly reduced, it may be that the matrix *metalloproteinases* are involved in this process. Batimastat may be a therapeutic modality for the treatment of colorectal cancer metastasis.

L18 ANSWER 17 OF 44 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:2486 HCAPLUS Full-text
DOCUMENT NUMBER: 114:2486
TITLE: Immunoassays for the detection of human collagenase, stromelysin, tissue *inhibitor* of *metalloproteinases* (TIMP) and enzyme-*inhibitor* complexes
AUTHOR(S): Cooksley, Susan; Hipkiss, Jayne B.; Tickle, Simon P.; *Holmes-Ievers, Eileen*; Docherty, Andrew J. P.; Murphy, Gillian; Lawson, Alastair D. G.
CORPORATE SOURCE: Dep. Immunochem., Celltech Ltd., Slough, SL1 4EN, UK
SOURCE: Matrix (Stuttgart) (*1990*), 10(5), 285-91
CODEN: MTRXEH; ISSN: 0934-8832
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Immunoassays were developed for human collagenase, stromelysin, tissue *inhibitor* of *metalloproteinases* (TIMP) and TIMP complexed with both of the active enzymes. The selection of antibodies of defined specificity enabled the measurement of both the pro and active forms of the *metalloproteinase*. Free TIMP was quantified by the selection of a monoclonal antibody which did not recognize TIMP when complexed with *metalloproteinases*. The detection of enzyme- *inhibitor* complexes was achieved by capturing the TIMP component of the complex and revealing the metalloenzyme using specific antibodies.

L18 ANSWER 18 OF 44 MEDLINE on STN
ACCESSION NUMBER: 2002357026 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 12099644
TITLE: Emerging biological therapies for pancreatic carcinoma.
AUTHOR: Gilliam Andrew D; *Watson Susan A*
CORPORATE SOURCE: Academic Unit of Cancer Studies, Department of Surgery Univertisy of Nottingham, Nottingham, NG7 2UH, UK.. andrew.gilliam@nottingham.ac.uk
SOURCE: European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, *(2002 Jun)* Vol. 28, No. 4, pp. 370-8. Ref: 105
Journal code: 8504356. ISSN: 0748-7983.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) General Review; (REVIEW)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 200208
ENTRY DATE: Entered STN: 9 Jul 2002
Last Updated on STN: 17 Aug 2002
Entered Medline: 16 Aug 2002

AB AIMS: The incidence of pancreatic carcinoma remains approximately equal to its mortality, with the vast majority of patients having advanced disease at presentation. This review is an update of the promising novel approaches involving biological therapy that may be used in conjunction with new chemotherapeutic agents in the near future. MEHTODS: A literature review was performed using the National Library of Medicine's Pubmed database, combined with recently published data from the AGA and ASCO conferences. RESULTS: Rapid progress is being made in gene and molecular technology potentially enabling us to ***inhibit*** pancreatic carcinogenesis and to reduce disease progression. Different targets include signal transduction ***inhibitors***, gene therapy, genetic prodrug activation therapy, antisense therapy, immunotherapy, matrix ***metalloproteinase*** and cyclo-oxygenase-2 ***inhibition*** and hormonal manipulation. CONCLUSION: A variety of biological agents are currently undergoing clinical trials, targeting different areas of the pancreas'neoplastic process. .

L18 ANSWER 19 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998143455 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9484924
TITLE: Phase I/II trial of batimastat, a matrix ***metalloproteinase inhibitor***, in patients with malignant ascites.
AUTHOR: Parsons S L; ***Watson S A***; Steele R J
CORPORATE SOURCE: Department of Surgery, University Hospital, Nottingham, UK.
SOURCE: European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology, ***(1997 Dec)*** Vol. 23, No. 6, pp. 526-31.
Journal code: 8504356. ISSN: 0748-7983.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 12 Mar 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 5 Mar 1998

AB Matrix ***metalloproteinases*** have been shown to be important in tumour invasion and metastasis, and the use of matrix ***metalloproteinase inhibitors*** in animal models has suggested that these agents may be useful in the control of malignant disease. This article reports the results of an early clinical trial of batimastat, one of the first generation of ***metalloproteinase inhibitors***, in patients with malignant ascites. The drug was well absorbed via the intraperitoneal route and associated with few side-effects. Furthermore, a response to treatment was seen in about half the evaluable patients with advanced malignant disease. The results suggest that further research on the use of matrix ***metalloproteinase inhibitors*** in patients with malignant disease is worthwhile.

L18 ANSWER 20 OF 44 MEDLINE on STN
ACCESSION NUMBER: 97204918 MEDLINE Full-text
DOCUMENT NUMBER: PubMed ID: 9052425
TITLE: Matrix ***metalloproteinases***.
AUTHOR: Parsons S L; ***Watson S A***; Brown P D; Collins H M; Steele R J
CORPORATE SOURCE: Department of Surgery, University Hospital, Nottingham, UK.
SOURCE: The British journal of surgery, ***(1997 Feb)*** Vol. 84, No. 2, pp. 160-6. Ref: 99
Journal code: 0372553. ISSN: 0007-1323.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199703
ENTRY DATE: Entered STN: 7 Apr 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 27 Mar 1997

AB BACKGROUND: The matrix ***metalloproteinases*** (MMPs) have a role in gastrointestinal malignancy. This role is reviewed, with particular reference to the gelatinase subgroup of enzymes. METHODS: All relevant papers derived from the Medline and Enbase databases between 1984 and early 1996 were reviewed. RESULT AND CONCLUSION: There is now strong evidence that MMPs play a major role in tumour invasion and metastasis. The development of MMP ***inhibitors*** may lead to important new treatment for the control of malignant disease.

L18 ANSWER 21 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2004:34085 BIOSIS Full-text
DOCUMENT NUMBER: PREV200400032181
TITLE: NOVEL ***INHIBITION*** OF MATRIX ***METALLOPROTEINASES***, ANGIOGENESIS, AND TUMOUR CELL INVASION BY CAPTOPRIL.
AUTHOR(S): Williams, Robert N. [Reprint Author]; Parsons, Simon [Reprint Author]; Rowlands, Brian [Reprint Author]; ***Watson, Susan*** [Reprint Author]
CORPORATE SOURCE: Nottingham, UK
SOURCE: Digestive Disease Week Abstracts and Itinerary Planner, (***2003***) Vol. 2003, pp. Abstract No. W964. e-file.
Meeting Info.: Digestive Disease 2003. FL, Orlando, USA. May 17-22, 2003. American Association for the Study of Liver Diseases; American Gastroenterological Association; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jan 2004
Last Updated on STN: 7 Jan 2004

AB Introduction: Angiotensin converting enzyme (ACE) is a zinc dependent metallopeptidase derived from the same family of enzymes as the matrix ***metalloproteinases*** (MMPs). These enzymes share structural homology, and their activity is ***inhibited*** by zinc binding compounds. Degradation of the extra cellular matrix (ECM) by MMPs is essential for tumour invasion and angiogenesis. MMP ***inhibition*** has been shown to reduce the invasive potential

of malignant cells and represents a therapeutic target. The ACE *inhibitor* Captopril, which has a known clinical safety profile, may exert an *inhibitory* effect on MMPs and thus possibly *inhibit* tumour cell invasion and angiogenesis.Aim: To investigate the effect of Captopril on the expression/activation of MMPs and its ability to *inhibit* angiogenesis and tumour cell invasion through extra cellular matrix.Method: Zymography was used to determine the effect of Captopril on the activity of MMP-2 & -9. Effects on MMP gene expression were analysed using real time reverse transcriptase PCR. The functional effect of MMP *inhibition* by Captopril on HT1080 tumour cell invasion was determined by matrigel invasion assay. Effects on angiogenesis were determined using TCS cellworks Angiokit containing human umbilical vein endothelial cells (HUVECs).Results: Captopril *inhibited* the activity of secreted MMP-2 and -9 in a dose dependent fashion. 5mM Captopril *inhibited* the activity of MMP-9 by 41.3% (p<0.001)) and pro-MMP-2 by 72.8% (p=0.014, whilst active MMP-2 was completely *inhibited*. Zymographic analysis of media conditioned by cells treated with 5mM Captopril showed that the activity of MMP-9, pro- and active MMP-2 was *inhibited* by 34.0% (p=0.009), 47.2% (p=0.004) and 33.7% (p=0.025) respectively. Real time PCR did not show any reduction in MMP gene expression with Captopril treatment. The *inhibition* of MMP activity by Captopril resulted in a functional reduction in the invasive capacity of HT1080 cells through matrigel. The number of invading cells was *inhibited* by 33.7% (p=0.000) with 5mM Captopril. Captopril also *inhibited* in vitro HUVEC angiogenesis by 27.7% (p=0.006).Conclusion: Captopril directly *inhibits* the activity of secreted MMPs but also *inhibits* MMP production at a post-transcriptional level. Furthermore, Captopril *inhibits* the invasion of MMP producing cells through synthetic ECM. The drug also demonstrates the ability to *inhibit* angiogenesis. Further work is currently underway to explore the possible therapeutic effects of Captopril on tumours in vivo..

L18 ANSWER 22 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:605314 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200605314
TITLE: Depletion of interstitial macrophages reduces interstitial fibrosis in experimental hydronephrosis.
AUTHOR(S): Kipari, Tiina M. J. [Reprint author]; Cailhier, Jean-Francois H. [Reprint author]; *Watson, Simon J. W.* [Reprint author]; Clay, Michael F. [Reprint author]; Lang, Richard; Hughes, Jeremy [Reprint author]
CORPORATE SOURCE: MRC Centre for Inflammation Research, University of Edinburgh, Edinburgh, UK
SOURCE: Journal of the American Society of Nephrology, (*September, 2002*) Vol. 13, No. Program and Abstracts Issue, pp. 541A. print.
Meeting Info.: Meeting of the American Society of Nephrology. Philadelphia, PA, USA. October 30-November 04, 2002. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Nov 2002
Last Updated on STN: 27 Nov 2002

L18 ANSWER 23 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:408933 BIOSIS Full-text

DOCUMENT NUMBER: PREV200200408933
TITLE: Glycine-extended gastrin can promote an increase in pro and active MMP-2 expression at the protein level in cells.
AUTHOR(S): Dean, Richard Asher [Reprint author]; Evans, Sean [Reprint author]; McWilliams, Dan [Reprint author]; *Watson, Sue A.* [Reprint author]
CORPORATE SOURCE: Cancer Studies Unit, Nottingham, UK
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (*March, 2002*) Vol. 43, pp. 535. print.
Meeting Info.: 93rd Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA. April 06-10, 2002.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 31 Jul 2002
Last Updated on STN: 23 Sep 2002

L18 ANSWER 24 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:509991 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200509991
TITLE: Increase in gene and protein expression of gastrin, CCK2R, MMP-2 and TIMP1 in Barrett's compared to paired normal samples.
AUTHOR(S): Harris, J. C. [Reprint author]; Dean, R. A. [Reprint author]; Clarke, P. A. [Reprint author]; Awan, A. [Reprint author]; Jankowski, J.; *Watson, S. A.* [Reprint author]
CORPORATE SOURCE: Academic Unit of Cancer Studies, QMC, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer, (*June, 2002*) Vol. 86, No. Supplement 1, pp. S48-S49. print.
Meeting Info.: British Cancer Research Meeting 2002. Glasgow, UK. June 30-July 03, 2002.
CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L18 ANSWER 25 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2002:509891 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200509891
TITLE: Captopril *inhibits* the matrix *metalloproteinases*: MMP-2 and MMP-9.
AUTHOR(S): Williams, R. N. [Reprint author]; Dean, R. A. [Reprint author]; Parsons, S. L.; Rowlands, B. J.; *Watson, S. A.* [Reprint author]
CORPORATE SOURCE: Academic Unit of Cancer Studies, QMC, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: British Journal of Cancer, (*June, 2002*) Vol. 86, No. Supplement 1, pp. S17. print.
Meeting Info.: British Cancer Research Meeting 2002. Glasgow, UK. June 30-July 03, 2002.

CODEN: BJCAAI. ISSN: 0007-0920.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Oct 2002
Last Updated on STN: 2 Oct 2002

L18 ANSWER 26 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2001:235183 BIOSIS Full-text
DOCUMENT NUMBER: PREV200100235183
TITLE: Co-culture of human squamous oesophageal and fibroblast cell lines in activation of proMMP-2 resulting in a down regulation of integrin alphaVbeta3 expression and MMP-2, MT1-MMP expression.
AUTHOR(S): Asher-Dean, R. [Reprint author]; Speake, W. J. [Reprint author]; Collins, H. M. [Reprint author]; Jankowski, J.; *Watson, S. A.* [Reprint author]
CORPORATE SOURCE: Cancer Studies Unit, Dept of Surgery, QMC, Nottingham, NG7 2UH, UK
SOURCE: Gut, (*March, 2001*) Vol. 48, No. Supplement 1, pp. A68-A69. print.
Meeting Info.: Annual Meeting of the British Society of Gastroenterology. Glasgow, Scotland. March 18, 2001-March 21, 2002. British Society of Gastroenterology.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 16 May 2001
Last Updated on STN: 18 Feb 2002

L18 ANSWER 27 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:201148 BIOSIS Full-text
DOCUMENT NUMBER: PREV200200201148
TITLE: Enhanced expression of TIMP-1 by Crohn's disease intestinal myofibroblasts: Potential mechanism by which isoforms of TGF-beta may lead to stricture formation.
AUTHOR(S): McKaig, Brian C. [Reprint author]; McWilliams, Dan; *Watson, Sue A.*; Mahida, Yashwant R.
CORPORATE SOURCE: Div of Gastroenterology, Univ Hosp, Nottingham, UK
SOURCE: Gastroenterology, (*April, 2001*) Vol. 120, No. 5 Supplement 1, pp. A.517. print.
Meeting Info.: 102nd Annual Meeting of the American Gastroenterological Association and Digestive Disease Week. Atlanta, Georgia, USA. May 20-23, 2001. American Gastroenterological Association; American Association for the Study of Liver Diseases; American Society for Gastrointestinal Endoscopy; Society for Surgery of the Alimentary Tract.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 20 Mar 2002
Last Updated on STN: 20 Mar 2002

L18 ANSWER 28 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN

ACCESSION NUMBER: 2000:230052 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000230052
TITLE: Expression of matrix *metalloproteinases* (MMPs) and tissue *inhibitors* of *metalloproteinases* (TIMPs) by human intestinal myofibroblasts (IMFs).
AUTHOR(S): Mckaig, B. [Reprint author]; Collins, H.; Hawkey, C. [Reprint author]; *Watson, S.*; Mahida, Y. [Reprint author]
CORPORATE SOURCE: Division of Gastroenterology, University Hospital, Nottingham, NG7 2UH, UK
SOURCE: Gut, (*April, 2000*) Vol. 46, No. 11, pp. A38. print.
Meeting Info.: 2000 Annual Meeting of the British Society of Gastroenterology. Birmingham, UK. March 21-23, 2000. British Society of Gastroenterology.
CODEN: GUTTAK. ISSN: 0017-5749.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 7 Jun 2000
Last Updated on STN: 5 Jan 2002

L18 ANSWER 29 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:257116 BIOSIS Full-text
DOCUMENT NUMBER: PREV200000257116
TITLE: Expression of matrix *metalloproteinases* (MMPs) and tissue *inhibitors* of *metalloproteinases* (TIMPs) by human intestinal myofibroblasts.
AUTHOR(S): McKaig, Brian C. [Reprint author]; Collins, Hilary; Hawkey, Christopher J.; *Watson, Sue*; Mahida, Yashwant R.
CORPORATE SOURCE: Div of Gastroenterology, Univ of Nottingham, Nottingham, UK
SOURCE: Gastroenterology, (*April, 2000*) Vol. 118, No. 4 Suppl. 2 Part 1, pp. AGA A551. print.
Meeting Info.: 101st Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Diego, California, USA. May 21-24, 2000. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Jun 2000
Last Updated on STN: 5 Jan 2002

L18 ANSWER 30 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:286830 BIOSIS Full-text
DOCUMENT NUMBER: PREV199800286830
TITLE: A phase II study of the oral matrix *metalloproteinase inhibitor*, marimastat, in patients with inoperable gastric cancer.
AUTHOR(S): Tierney, G.; Parsons, S. L.; Griffin, N. R.; *Watson, S. A.*; Steele, R. J. C.
CORPORATE SOURCE: Dep. Surg., Univ. Hosp., Nottingham, UK
SOURCE: Gastroenterology, (*April 15, 1998*) Vol. 114, No. 4 PART 2, pp. A688. print.
Meeting Info.: Digestive Disease Week and the 99th Annual

Meeting of the American Gastroenterological Association. New Orleans, Louisiana, USA. May 16-22, 1998. American Gastroenterological Association.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 8 Jul 1998
Last Updated on STN: 13 Aug 1998

L18 ANSWER 31 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1997:279462 BIOSIS Full-text
DOCUMENT NUMBER: PREV199799578665
TITLE: A phase i/ii study of oral matrix ***metalloproteinase inhibitor***, marimastat, in patients with inoperable gastric cancer.
AUTHOR(S): Parsons, S. L.; ***Watson, S. A.***; Griffin, N. R.; Tierney, G. M.; Steele, R. J. C.
CORPORATE SOURCE: Dep. Surgery Pathol., Univ. Hosp., Nottingham, UK
SOURCE: Gastroenterology, (***1997***) Vol. 112, No. 4 SUPPL., pp. A636.
Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association. Washington, D.C., USA. May 11-14, 1997.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 3 Jul 1997
Last Updated on STN: 5 Aug 1997

L18 ANSWER 32 OF 44 BIOSIS COPYRIGHT (c) 2007 The Thomson Corporation on STN
ACCESSION NUMBER: 1996:299159 BIOSIS Full-text
DOCUMENT NUMBER: PREV199699021515
TITLE: Phase I/II trial of a matrix ***metalloproteinase inhibitor*** in patients with malignant ascites.
AUTHOR(S): Parsons, S. L.; ***Watson, S. A.***; Amar, S. S.; Steele, R. J. C.
CORPORATE SOURCE: Dep. Surg., Univ. Hosp., Nottingham NG7 2UH, UK
SOURCE: Gastroenterology, (***1996***) Vol. 110, No. 4 SUPPL., pp. A575.
Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week. San Francisco, California, USA. May 19-22, 1996.
CODEN: GASTAB. ISSN: 0016-5085.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 2 Jul 1996
Last Updated on STN: 2 Jul 1996

L18 ANSWER 33 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2003-27672 DRUGU B P Full-text
TITLE: ***Inhibition*** of matrix ***metalloproteinase*** 2 and 9 by the angiotensin converting enzyme ***inhibitor*** captopril.
AUTHOR: Williams R N; Dean R A; Parsons S L; Rowlands B J; ***Watson S A***

CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Surg. (90, No. 5, 617, 2003)
CODEN: BJSUAM ISSN: 0007-1323
AVAIL. OF DOC.: Academic Unit of Cancer Studies, Department of Surgery, University of Nottingham, Nottingham, U.K.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2003-27672 DRUGU B P Full-text
AB Matrix ***metalloproteinase*** (MMP) gene expression in human fibrosarcoma cells in-vitro was not affected by captopril (0.25-5 mM). The activity of secreted MMPs was reduced dose-dependently with the maximal effect seen at 5 mM. Pro-MMP-2 and MMP-9 activity were reduced by 72.8% and 41.3%, respectively and active MMP-2 was abolished. Cellular production of MMPs was reduced by 5 mM captopril with Pro-MMP-2 and MMP-9 reduced by 47.2% and 33.7% respectively with a 40.0% reduction in active MMP-2. HT-1080 tumors were implanted in nude mice to determine the effect of Captopril (200 mg/kg) on tumor growth. The in-vivo growth of HT1080 was ***inhibited*** by 53.5%. Captopril ***inhibits*** MMP production and activation which translates into a therapeutic action on in vivo tumor growth. (conference abstract: 3rd Meeting of the Society of Academic and Research Surgery, Leeds, U.K., January, 2003). (No EX).
ABEX (KL)

L18 ANSWER 34 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2004-20928 DRUGU P Full-text
TITLE: Novel ***inhibition*** of matrix ***metalloproteinases***, angiogenesis, and tumour cell invasion by captopril.
AUTHOR: Williams R N; Parsons S; Rowlands B; ***Watson S***
LOCATION: USA
SOURCE: ; Digestive Dis. Week (106925, 2003)
CODEN: ; 9999
AVAIL. OF DOC.: No Reprint Address.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2004-20928 DRUGU P Full-text
AB In-vitro, captopril ***inhibited*** matrix ***metalloproteinases*** (MMP), angiogenesis and tumor cell invasion through extracellular matrix. (conference abstract: Digestive Disease Week 2003, Orlando, Florida, USA, May 18-21, 2003).
ABEX Methods Zymography was used to determine effect of captopril on activity of MMP-2 and MMP-9. Effects on MMP gene expression were analyzed using real-time reverse transcriptase PCR. Functional effect of MMP ***inhibition*** by captopril on HCT1080 cell invasion was determined by matrigel invasion assay. Effects on angiogenesis were determined using TCS cellworks Angiokit containing human umbilical vein endothelial cells (HUVEC). Results Captopril ***inhibited*** activity of secreted MMP-2 and MMP-9 in a dose-dependent manner. In particular, 5 mM captopril ***inhibited*** activity of MMP-9 by 41.3% and pro-MMP-2 by 72.8%, while active MMP-2 was completely ***inhibited***. Zymographic analysis of media conditioned by cells exposed to 5 mM captopril demonstrated that activity of MMP-9, pro-MMP-2 and active MMP-2 was ***inhibited*** by 34.0%, 47.2% and 33.7%, respectively. Real-time PCR did not demonstrate any down-regulation of MMP gene expression with captopril. ***Inhibition*** of MMP activity by captopril caused a functional reduction in invasive capacity of HT1080 cells through matrigel. Number of invading cells was decreased by 33.7%

with 5 mM captopril. Captopril also *inhibited* HUVEC angiogenesis by 27.7%. (E42/JM)

L18 ANSWER 35 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 2002-32707 DRUGU P B Full-text
TITLE: Captopril *inhibits* the matrix *metalloproteinases*: MMP-2 and MMP-9.
AUTHOR: Williams R N; Dean R A; Parsons S L; Rowlands B J; *Watson S A*
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Cancer (86, Suppl. 1, S17, 2002)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Academic Unit of Cancer Studies, University Hospital, Nottingham, NG7 2UH, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 2002-32707 DRUGU P B Full-text
AB The effect of captopril on the matrix *metalloproteinases* MMP-2 and MMP-9 was investigated in HT1080 cells in-vitro. The results suggested that captopril *inhibited* MMP-2 and MMP-9, by binding to their active site. The *inhibition* of MMP activity produced by captopril in cell culture was greater than its *inhibitory* effect on cell proliferation. This suggests that captopril may *inhibit* other cellular pathways and that the reduction in MMP activity was not only a reflection of the reduction in cell population. (conference abstract: British Cancer Research Meeting, Glasgow, U.K., 2002).
ABEX Gelatin zymography was used to investigated captopril *inhibition* of MMP-2 and MMP-9. Captopril *inhibited* both MMP-2 and -9 dose-dependently when added to zymography developing buffer. MMP-9 was *inhibited* to 70.7%, 64.8% and 46.9% of control values by 500 uM, 1 mM and 2.5 mM captopril, respectively. Active MMP-2 was *inhibited* to 23.4% and 9.3% by 250 uM and 500 uM captopril, respectively. The addition of 5 mM captopril to cell culture of HT1080 produced *inhibition* of MMP-9 activity to 65% of control values and 75% of control values for active MMP-2 activity. Captopril at 5 mM *inhibited* the proliferation of HT1080 cells. The population of cells treated with 5 mM captopril was only 84% of the untreated control population. (DAC)

L18 ANSWER 36 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-43928 DRUGU P B Full-text
TITLE: Therapeutic effect of the matrix *metalloproteinase* (MMP) *inhibitor*, marimastat, in a gastric cancer xenograft model: relationship to MMP messenger RNA levels.
AUTHOR: Tierney G M; Collins H M; Morris T M; Scholefield J H; *Watson S A*
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Surg. (85, No. 11, 1562, 1998)
CODEN: BJSUAM ISSN: 0007-1323
AVAIL. OF DOC.: Academic Unit of Cancer Studies, Division of Gastrointestinal Surgery, University of Nottingham, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-43928 DRUGU P B Full-text

AB The effect of marimastat (MM) on the growth and MMP expression of human gastric xenografts, MKN45G and ST-16, was evaluated in mice and any observed effect was related to a change in MMP mRNA level. Results showed that MM caused ST-16 xenografts to become macroscopically undetectable. (conference abstract).
ABEX Methods MKN45G and ST-16 tissue was s.c. implanted into nude mice. MM (50 mg/kg) was administered daily, and animals were sacrificed at day 28. Xenograft tissue was extracted, and mRNA was evaluated using PCR. Results ST-16 tumors were not detected macroscopically after MM treatment.reverse-transcriptase PCR demonstrated mRNAs for MMP-2, MMP-7 and MMP-9, tissue inhibitors of MMPs (TIMPs) 1 and 2, and MT-MMP-1 in all control samples. MKN45G showed a significant reduction in mRNA for MT-MMP-1 after treatment. (KH)

L18 ANSWER 37 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1999-01111 DRUGU P Full-text
TITLE: Therapeutic effect of the matrix *metalloproteinase inhibitor*, marimastat in a gastric cancer xenograft model: relationship to CEA levels.
AUTHOR: *Watson S A*; Morris T M; Collins H M; Tierney G; Bawden L J; Hawkins K
CORPORATE SOURCE: Univ.Nottingham; British-Biotech.
LOCATION: Nottingham, U.K.
SOURCE: Br.J.Cancer (78, Suppl. 1, 50, 1998)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Academic Unit of Cancer Studies, Division of GI Surgery, University of Nottingham, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1999-01111 DRUGU P Full-text
AB The effect of the broad spectrum MMP inhibitor marimastat was studied on the growth of a CEA-secreting human gastric xenograft, MGLVA1, allowing any relationship between therapeutic effect and serum CEA levels to be determined in mice. Marimastat was shown to significantly inhibit tumor size in both male and female mice when compared with the respective vehicle controls.
ABEX For the therapy experiments MGLVA1 tissues was implanted s.c. into both male and female nude mice. Dosing with marimastat (15 mg/ml in osmotic pump is equivalent to approximately 7.2 mg/kg/day) began on day 1 and continued throughout the course of the experiment. Marimastat was shown to significantly inhibit tumor size in both male and female mice when compared with the respective vehicle controls. Marimastat also exerted a significant effect of survival with median survival increasing from 18 days to 30 days. A further experiment was designed to asses the effect of marimastat in circulating CEA levels. Marimastat or vehicle was delivered as above, and the ability of marimastat to significantly inhibit tumor growth was confirmed. Throughout the course of the experiment 4 animals of each sex from both treated and control groups were sacrificed at regular intervals and serum samples were collected for CEA analysis. The log of CEA concentration was linearly related to log of the tumor weight, irrespective of whether the tumor derives from a marimastat or vehicle treated animal. (KJ)

L18 ANSWER 38 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-45299 DRUGU T P S Full-text
TITLE: A phase II study of the oral matrix *metalloproteinase inhibitor*, marimastat, in patients with inoperable gastric cancer.
AUTHOR: Tierny G; Parsons S L; Griffin N R; *Watson S A*;

Steele R J C
LOCATION: Nottingham, U.K.
SOURCE: Gastroenterology (114, No. 4, Pt. 2, A688, 1998)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Department of Surgery, University Hospital, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-45299 DRUGU T P S Full-text
AB The matrix ***metalloproteinases*** (MMPs) are a family of proteolytic enzymes involved in turnover of the extracellular matrix and have been implicated in the process of tumor growth and metastasis. The aim of this study was to confirm the safety of a 4 wk course of marimastat, to assess the tumors at endoscopy and examine biopsies histologically, to quantify tumor MMPs prior to and after treatment in 25 patients with advanced gastric adenocarcinoma. The side-effects were musculoskeletal, appeared dose-related and resolved after a treatment break. The study demonstrated good oral bioavailability of marimastat. Side-effects appear dose-related and reversible. These effects may be due to ***inhibition*** of collagenase in peri-articular tissues. A prospective, randomized, placebo-controlled study of this treatment is currently underway. (conference abstract).
ABEX The aim of this study was to confirm the safety of a 4 wk course of marimastat, to assess the tumors at endoscopy and examine biopsies histologically and using zymography, to quantify tumor MMPs prior to and after treatment. 25 Patients with advanced gastric adenocarcinoma underwent pre-dose endoscopy and biopsy of the tumor. They received marimastat at a dose of 50 mg b.i.d. (1st 6 patients) or 25 mg once daily (all subsequent patients). Endoscopy was performed at day 28. Patients with a response to the treatment or static disease in the absence of side-effects were selected to continue. Biopsies were sent for histology and gelatin zymography. Both doses gave adequate plasma drug levels (mean trough level: 260 u/l on 50 mg, b.d., 50 u/l on 25 mg, o.d.). 15 Patients had continued use of the drug, 9 on the basis of response (defined as decreased tumor vascularity, evidence of stroma formation or decreased size). The side-effects were musculoskeletal; arose after 28 days of treatment, appeared dose-related and resolved after a treatment break. There was no difference in the zymography profile after treatment. This study has demonstrated good oral bioavailability of marimastat. Side-effects appear dose-related and reversible. These effects may be due to ***inhibition*** of collagenase in peri-articular tissues. A prospective, randomized, placebo-controlled study of this treatment is currently underway. (LJ)

L18 ANSWER 39 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1997-26528 DRUGU T S Full-text
TITLE: A phase I/II study of the oral matric ***metalloproteinase inhibitor***, marimastat, in patients with inoperable gastric cancer.
AUTHOR: Parsons S L; ***Watson S*** A; Griffin N R; Tierney G M; Steele R J C
LOCATION: Nottingham, U.K.
SOURCE: Gastroenterology (112, No. 4, Suppl., A636, 1997)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Department of Surgery and Pathology, University Hospital, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT

FILE SEGMENT: Literature
AN 1997-26528 DRUGU T S Full-text
AB Matrix ***metalloproteinases*** (MMPs) play an important role in tumor invasion and metastasis. Marimastat (SC-44463) is the 1st p.o. active synthetic MMP ***inhibitor*** and was given to 14 patients with inoperable gastric cancer, in a phase I/phase II study. Musculoskeletal pain and restriction of movement were identified as the principle treatment-related side-effects and led to a reduction in dose. It is concluded that a dose of 25 mg/day appears to be well-tolerated in patients with inoperable gastric cancer. There are early indications that marimastat may slow the rate of progression of gastric cancer. (conference abstract).
ABEX MMPs play an important role in tumor invasion and metastasis. Marimastat is the 1st orally active synthetic MMP ***inhibitor*** and was given to 14 patients for 28 days. An endoscopic examination and biopsy was performed at entry and at 28 days of treatment. Safety and tolerability were assessed and biopsy samples analyzed histologically. Patients who showed no evidence of progression endoscopically were eligible for continued treatment. 14 Patients completed the 28 day study period (median age 70.4 yr, range 45-85, 9 male). 7 Patients showed no evidence of progression at the 28 day endoscopic examination and continued to take marimastat. 2 Patients showed histological and macroscopic changes in tumor appearance with decreased tumor cellularity and increased stromal tissue for 15 and 4 mth, respectively. Macroscopic changes consistent with stromal formation were observed in the tumors of 3 other patients. Musculoskeletal pain and restriction of movement were identified as the principle treatment-related side-effects and led to a reduction in dose. A dose of 25 mg/day appears to be well-tolerated in patients with inoperable gastric cancer. There are early indications that marimastat may slow the rate of progression of gastric cancer. (LJ)

L18 ANSWER 40 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1998-03614 DRUGU B T Full-text
TITLE: Gelatinase profile in advanced gastric cancer before and after treatment with a matrix ***metalloproteinase inhibitor***.
AUTHOR: Tierney G; Collins H M; Parsons S; ***Watson S***; Steele R J C
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Gut (41, Suppl. 3, A151, 1997)
CODEN: GUTTAK ISSN: 0017-5749
AVAIL. OF DOC.: Dept. of Surgery, University Hospital, Nottingham, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1998-03614 DRUGU B T Full-text
AB Marimastat (BB-2516; British-Biotech.) did not affect the enzyme profile of a gastric cancer biopsy obtained from patients who received the drug, a matrix ***metalloproteinases inhibitor***, as part of a phase II trial. The 92 kDa and the 72 kDa gelatinases were expressed in the tumor biopsies both prior to and after treatment with marimastat. Their active forms (82 kDa and 62 kDa) were also identified on the gels. After treatment there was no significant change in the quantity of active or inactive enzyme. These results indicate that marimstat does not convert the malignant-associated gelatinase to the benign form of enzyme. (conference abstract). (No EX.).
ABEX (VH)

L18 ANSWER 41 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-30339 DRUGU P Full-text

TITLE: Combined therapeutic effect of marimastat and cisplatin on the in vivo growth of a human small cell lung cancer.
AUTHOR: ***Watson S A***; Morris T M; Parsons S; Steele R J C; Drummond A; Brown P
CORPORATE SOURCE: Univ.Nottingham; British-Biotechnol.
LOCATION: Nottingham; Oxford, U.K.
SOURCE: Br.J.Cancer (73, Suppl. 26, 29, 1996)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Cancer Studies Unit, Department of Surgery, University of Nottingham NG7 2UH, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1996-30339 DRUGU P Full-text
AB Combined antitumor effects of the matrix ***metalloproteinase*** (MMP) ***inhibitor***, p.o. marimastat (SC-44463, MS), with i.v. cisplatin (CP), were evaluated against human small cell lung tumor xenografts in nude mice. The observed increased therapeutic effectiveness with the combination may have been the result of the 2 agents ***inhibiting*** tumor growth through independent mechanisms. (conference abstract).
ABEX Overproduction of MMPs appears to play an important role in tumor metastasis due to an increased ability to both break down the basement membrane and promote neo-vascularization. Thus ***inhibitors*** of such enzymes may have a therapeutic role. The human small cell lung tumor line, 841, has been shown to express the 92 and 72kDa forms of gelatinase by zymography and be sensitive to the antiproliferative effects of cisplatin. Thus, it was decided to evaluate both the individual and combined effects of MS (50 mg/kg, b.i.d.) and CP (4 mg/kg) on the subcutaneous growth of 841 tumors in MF1 nude mice. At day 20, the cross-sectional area of tumors in the vehicle control group (mean of 265.0 sq.m) were significantly greater than in the MS-treated group (190.3 sq.m), the CP group (101.5 sq.m) and the combination (57.6 sq.m). The combination was significantly smaller than the 2 treatments given individually. The time taken for tumors to reach a size greater than 300 sq.m was evaluated for each treatment group. Vehicle control-treated animals were terminated by day 31 compared to day 38 for MS alone, day 43 for CP and day 70 for animals treated with the combination. (E54/RSV)

L18 ANSWER 42 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-38650 DRUGU T P S Full-text
TITLE: Phase I/II trial of a matric ***metalloproteinase inhibitor*** in patients with malignant ascites.
AUTHOR: Parsons S L; ***Watson S A***; Amar S S; Steele R J C
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Gastroenterology (110, No. 4, Suppl., A575, 1996)
CODEN: GASTAB ISSN: 0016-5085
AVAIL. OF DOC.: Department of Surgery, University Hospital, Nottingham, England, NG7 2UH.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1996-38650 DRUGU T P S Full-text
AB In a phase I/II trial, 9 patients (pts) with malignant ascites underwent i.p. administration of a suspension of a synthetic matrix ***metalloproteinase inhibitor*** (Batimastat) after removal of an equal volume of ascites. Rapid systemic drug absorption was achieved with drug levels remaining elevated for

6 wk and were higher than in a corresponding study where the ascites was drained to dryness prior to drug administration. Side-effects consisted of abdominal pain, scrotal edema, pyrexia, nausea and vomiting. A treatment response was seen in most pts. Thus, i.p. Batimastat is well absorbed and the large Vd (ascites not drained) improved absorption. Our results suggest that this agent may be useful in controlling ascites though further studies are required to confirm this. (conference abstract).
ABEX Methods 9 Pts with proven malignant ascites were recruited and underwent i.p. administration of a 500 ml suspension of Batimastat after removal of an equal volume of ascites. Response to treatment was assessed by weight, abdominal girth and drainage. Results Rapid systemic drug absorption was achieved with drug levels remaining elevated for 6 wk and were higher than in a corresponding study where the ascites was drained to dryness prior to drug administration. Side-effects consisted of abdominal pain of mild-to-moderate intensity (6 pts), pyrexia (2 pts), nausea (3 pts) and vomiting (2 pts). Only abdominal pain (3 pts) and scrotal oedema continued beyond 72 hr. A treatment response was seen in 5/9 patients. (SA)

L18 ANSWER 43 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1996-18382 DRUGU T B S Full-text
TITLE: Phase I/II trial of a matrix ***metalloproteinase inhibitor*** in patients with malignant ascites.
AUTHOR: Parsons S L; ***Watson S A***; Amar S S; Steele R J C
CORPORATE SOURCE: Univ.Nottingham
LOCATION: Nottingham, U.K.
SOURCE: Gut (38, Suppl. 1, A18, 1996)
CODEN: GUTTAK ISSN: 0017-5749
AVAIL. OF DOC.: Department of Surgery, University Hospital, Nottingham, England NG7 20H.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1996-18382 DRUGU T B S Full-text
AB Intraperitoneal Batimastat successfully controlled ascites in 9 patients with malignant ascites in a phase I/II trial. Side-effects included abdominal pain of mild to moderate intensity, pyrexia, nausea and vomiting. A treatment response was seen in 5/9 patients. Intraperitoneal Batimastat was well absorbed and the large volume of dissolution (ascites not drained) improved absorption. Batimastat may be useful in controlling ascites though further studies are required to confirm this. (conference abstract).
ABEX Nine patients with malignant ascites underwent intraperitoneal administration of a 500 ml suspension of Batimastat after removal of an equal volume of ascites. Response to treatment was assessed by weight, abdominal girth and drainage. Rapid systemic drug absorption was achieved. Drug levels remained elevated for 6 weeks. Only abdominal pain and scrotal edema continued beyond 72 hr. (COS)

L18 ANSWER 44 OF 44 DRUGU COPYRIGHT 2007 THE THOMSON CORP on STN
ACCESSION NUMBER: 1994-23213 DRUGU P Full-text
TITLE: The matrix ***metalloproteinase inhibitor*** BB94 ***inhibits*** experimental metastasis and ascites formation of the human colorectal tumour, C170HM2.
AUTHOR: ***Watson S A***; Brown P D; Morris T M; Robinson G; Hardcastle J D
LOCATION: Nottingham, Oxford, United Kingdom
SOURCE: Br.J.Cancer (69, Suppl. 21, 19, 1994)
CODEN: BJCAAI ISSN: 0007-0920
AVAIL. OF DOC.: Department of Surgery, Queen's Medical center, Nottingham,

NG7 2RD, England.
LANGUAGE: English
DOCUMENT TYPE: Journal
FIELD AVAIL.: AB; LA; CT
FILE SEGMENT: Literature
AN 1994-23213 DRUGU P Full-text
AB Matrix ***metalloproteinases*** are known to play a role in the progression of human colorectal cancer. In the present study, the ***metalloproteinase inhibitor***, BB94, given by the i.p. route, ***inhibited*** experimental metastasis and ascites formation of a human colorectal tumor cell-line, C170HM2, in nude mice. Agents which ***inhibit*** the activity of invasive enzymes may reduce tumor spread and may therefore be of clinical value. (congress abstract).
ABEX C170HM2 has been selected to invade the liver following i.p. injection into nude mice. The C170HM2 tumors express both interstitial collagenase, at the leading edge of the tumor, and 72kDa gelatinase, during invasion within the liver. BB94 was administered at a dose of 40 mg/kg, i.p., from day 10 to the end of the study (day 39) and was shown to significantly reduce both the number (35% of vehicle-treated controls) and the cross-sectional area (73% of control) of the liver tumors. Histological analysis showed that the zone of proliferative cells was reduced and necrosis within the tumors was more advanced in the BB94-treated group. An ascites variant of C170HM2 has been derived in SCID mice following i.p. administration of cells. BB94 given from day 0, at the same dosage schedule as described, reduced (i) the number of mice developing ascites from 100% to 53%; (ii) the mean ascites volume from 1.78 ml to 0.38 ml; and (iii) peritoneal tumor weight from 2.19 g to 1.70 g. All the in-vivo studies were performed according to the UK coordinating committee for Cancer Research Guidelines. (NPH)

**********RESULTS FROM QUERY**********

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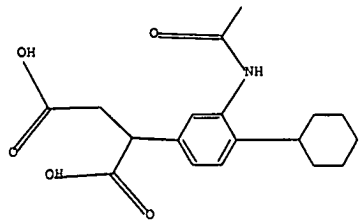

Structure attributes must be viewed using STN Express query preparation.
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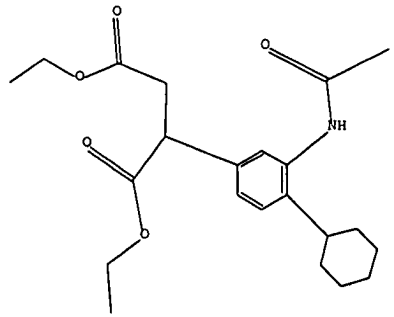

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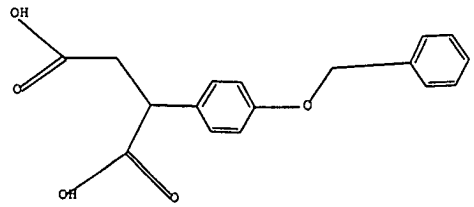

Structure attributes must be viewed using STN Express query preparation.
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L30 4 SEA FILE=REGISTRY SSS FUL L22
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L40 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L28
L41 1 SEA FILE=HCAPLUS ABB=ON PLU=ON L33
L42 3 SEA FILE=HCAPLUS ABB=ON PLU=ON L30
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=> d que 168
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L60 549 SEA FILE=REGISTRY ABB=ON PLU=ON C22 H31 N O5/MF
L61 1469 SEA FILE=REGISTRY ABB=ON PLU=ON C18 H23 N O5/MF

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L65       25598 SEA FILE=HCAPLUS ABB=ON   PLU=ON  METALLOPROTEINASE?
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=> d que 190
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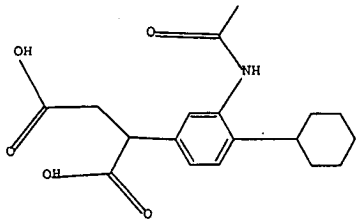


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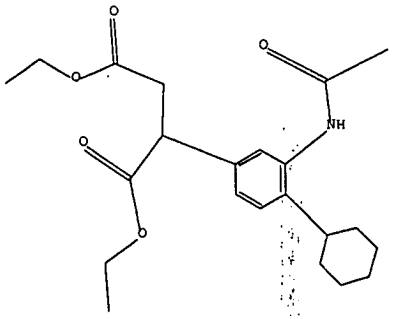


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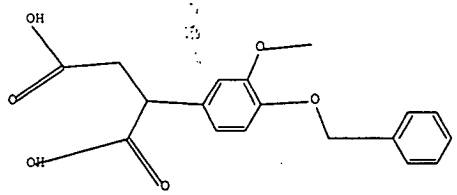


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Structure attributes must be viewed using STN Express query preparation.
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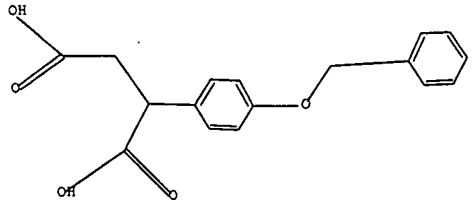


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Structure attributes must be viewed using STN Express query preparation.
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USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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PROCESSING COMPLETED FOR L43
PROCESSING COMPLETED FOR L68
PROCESSING COMPLETED FOR L90
L91          33 DUP REM L43 L68 L90 (1 DUPLICATE REMOVED)
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L91  ANSWER 1 OF 33  HCAPLUS  COPYRIGHT 2007 ACS on STN DUPLICATE 1
ACCESSION NUMBER:        1995:994182  HCAPLUS  Full-text
DOCUMENT NUMBER:         124:56708
TITLE:                   Preparation of N-acylated amino acid amide derivatives
                         as metalloproteinase inhibitors.
INVENTOR(S):             Beckett, Raymond Paul; Whittaker, Mark; Miller,
                         Andrew; Martin, Fionna Mitchell
PATENT ASSIGNEE(S):      British Biotech Pharmaceuticals Ltd., UK
SOURCE:                  PCT Int. Appl., 94 pp.
                         CODEN: PIXXD2
DOCUMENT TYPE:           Patent
LANGUAGE:                English
FAMILY ACC. NUM. COUNT:  1
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
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     WO 9519956           A1    19950727    WO 1995-GB111          19950120 <--
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     GB 2316078           B     19980603
     AT 165817            T     19980515    AT 1995-906396         19950120 <--
     ES 2117400           T3    19980801    ES 1995-906396         19950120 <--
     RU 2136657           C1    19990910    RU 1996-117034         19950120 <--
     AT 190609            T     20000415    AT 1997-117543         19950120 <--
     ES 2144819           T3    20000616    ES 1997-117543         19950120 <--
     PT 822186            T     20000831    PT 1997-117543         19950120 <--
     PL 179997            B1    20001130    PL 1995-315745         19950120 <--
     SK 281544            B6    20010409    SK 1996-941            19950120 <--
     CZ 290145            B6    20020612    CZ 1996-2115           19950120 <--
     IN 1995MA00820       A     20050225    IN 1995-MA820          19950714 <--
     FI 9602904           A     19960719    FI 1996-2904           19960719 <--
     NO 9603030           A     19960919    NO 1996-3030           19960719 <--
     NO 306396            B1    19991101
     US 5747514           A     19980505    US 1996-685330         19960719 <--
     US 5859253           A     19990112    US 1998-25943          19980219 <--
     US 5919940           A     19990706    US 1998-174252         19981016 <--
     GR 3033209           T3    20000831    GR 2000-400903         20000412 <--
PRIORITY APPLN. INFO.:                       GB 1994-1034       A   19940120 <--
                                             GB 1994-15619      A   19940802 <--
                                             EP 1995-906396     A3  19950120 <--
                                             GB 1996-11280      A3  19950120 <--
                                             WO 1995-GB111      W   19950120 <--
                                             US 1996-685330     A3  19960719 <--
                                             US 1998-25943      A3  19980219 <--
OTHER SOURCE(S):         MARPAT 124:56708
GI
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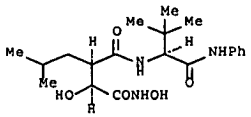


I

```
AB   XR1CHCHR2CONHCHR3CONR4R5 [X = CO2H, CONHOH; R1 = H, alkyl, alkenyl,
     (substituted) Ph, phenylalkyl, heterocyclyl, heterocyclylalkyl, etc.; R2 =
     (substituted) alkyl, alkenyl, alkynyl, phenylalkyl, heteroarylalkyl,
     cycloalkylalkyl, cycloalkenylalkyl; R3 = (protected) characterizing group of a
     natural or nonnatural amino acid; R4 = (substituted) Ph, 5- or 6-membered
     heteroaryl and N-oxides thereof, which may be optionally fused to a benzene
     ring or to a 5-, 6- or 7-membered heterocyclic ring], were prepared  Thus,
     title compound (I) (solution phase preparation given) inhibited collagenase,
     72 kDa gelatinase, and stromelysin with IC50 = 2 nM, 5 nM, and 9 nM, resp.
IT   9001-12-1, Collagenase 79955-99-0, Stromelysin
     146480-35-5, Gelatinase A
     RL: BPR (Biological process); BSU (Biological study, unclassified); MSC
     (Miscellaneous); BIOL (Biological study); PROC (Process)
        (inhibitors; preparation of N-acylated amino acid amide derivs. as
        metalloproteinase inhibitors)
```

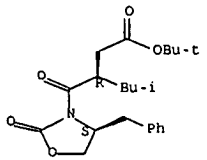
RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 79955-99-0 HCAPLUS
CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of N-acylated amino acid amide derivs. as *metalloproteinase inhibitors*)
RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

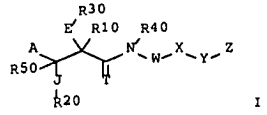
Absolute stereochemistry.



L91 ANSWER 2 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:796760 HCAPLUS Full-text
DOCUMENT NUMBER: 145:230531
TITLE: Preparation of tartaric acid functional compounds for the treatment of inflammatory disorders mediated by MMPs, aggrecanase, ADMP, LpxC, ADAMs, TACE and TNF-α
INVENTOR(S): Siddiqui, M. Arshad; Mansoor, Umar Faruk; Reddy, Panduranga A.; Madison, Vincent S.
PATENT ASSIGNEE(S): Schering Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 523pp., Cont.-in-part of U.S. Ser. No. 142,601.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006178366	A1	20060810	US 2005-291595	20051201 <--
US 2006252778	A1	20061109	US 2005-142601	20050601 <--

PRIORITY APPLN. INFO.: US 2004-576153P P 20040602 <--
US 2005-142601 A2 20050601
OTHER SOURCE(S): MARPAT 145:230531
GI



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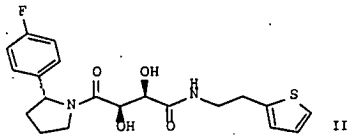


II

AB The title compds. I [A = (un)substituted benzimidazol-2-yl, imidazol-2-yl, CONH2, CSNH2, etc.; J, E = O, S, NR5 (wherein R5 = H, alkyl, alkylaryl); T = O, S; R10, R20 = H, alkyl, fluoroalkyl; R30 = H, alkyl or R30 and R40, taken together with N to which R40 is attached, are joined to form 4-7 membered (un)substituted heterocyclyl; R40, R50 = H, alkyl; W = [C(R13)2]n (wherein n = 0-5 or a bond; R13 = H, halo, OH, etc.); X = a bond, alkyl, cycloalkyl, etc.; Y = a bond, O, S, NH, etc.; Z = H, alkyl, aryl, etc.; or their pharmaceutically acceptable salts] which can be useful for the treatment of diseases or conditions mediated by MMPs, aggrecanase, ADMP, LpxC, ADAMs, TACE and TNF-α, were prepared E.g., a multi-step synthesis of II, starting from 2,2-dimethyl-[1,3]dioxolane-4R,5R- dicarboxylic acid monomethyl ester and 2-(thien-1-yl)ethylamine, was given. The compds. I were tested against LpxC and ADMP (biol. data given for representative compds. I).
IT *141907-41-7 151769-16-3*, Tumor necrosis factor-converting enzyme
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of tartaric acid functional compds. for treating inflammatory disorders mediated by MMPs, aggrecanase, ADMP, LpxC, ADAMs, TACE and TNF-α)
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

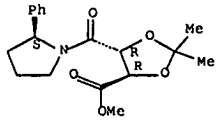
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 151769-16-3 HCAPLUS
CN Proteinase, pro-tumor necrosis factor (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *871719-73-2P 871723-66-9P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of tartaric acid functional compds. for treating inflammatory disorders mediated by MMPs, aggrecanase, ADMP, LpxC, ADAMs, TACE and

TNF-α)

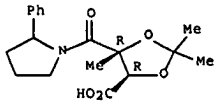
RN 871719-73-2 HCAPLUS
CN 1,3-Dioxolane-4-carboxylic acid, 2,2-dimethyl-5-[[(2S)-2-phenyl-1-pyrrolidinyl]carbonyl]-, methyl ester, (4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 871723-66-9 HCAPLUS
CN 1,3-Dioxolane-4-carboxylic acid, 2,2,5-trimethyl-5-[(2-phenyl-1-pyrrolidinyl)carbonyl]-, (4R,5R)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 3 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:182646 HCAPLUS Full-text
DOCUMENT NUMBER: 142:280227
TITLE: Preparation of hydroxamates as matrix *metalloproteinase inhibitors*
INVENTOR(S): Pain, Gilles; Davies, Stephen John; Bombrun, Agnes
PATENT ASSIGNEE(S): Vernalis Oxford Limited, UK; Laboratoires Serono S.A.
SOURCE: PCT Int. Appl., 89 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

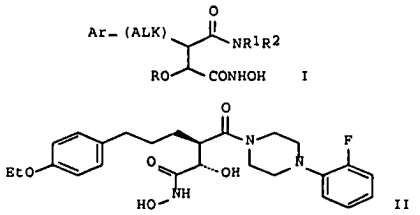
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005019194	A1	20050303	WO 2004-GB3558	20040818 <--

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK,

EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

AU 2004266896	A1	20050303	AU 2004-266896	20040818 <--
CA 2536576	A1	20050303	CA 2004-2536576	20040818 <--
EP 1660471	A1	20060531	EP 2004-768117	20040818 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007503422	T	20070222	JP 2006-524410	20040818 <--
CN 1930139	A	20070314	CN 2004-80023748	20040818 <--
NO 2006001302	A	20060519	NO 2006-1302	20060322 <--
US 2006281920	A1	20061214	US 2006-568433	20060808 <--
PRIORITY APPLN. INFO.:			GB 2003-13917 A	20030823 <--
			GB 2003-28632 A	20031210 <--
			WO 2004-GB3558 W	20040818 <--

OTHER SOURCE(S): CASREACT 142:280227; MARPAT 142:280227
GI



AB Title compds. I [wherein Ar = (un)substituted (hetero)aryl or (hetero)cycloalkyl; R = H or (cyclo)alkyl; Alk = alkylene or alkenylene; R1 and R2 link together to form (un)substituted heterocycloalkyl rings which is optionally fused to (un)substituted (hetero)cycloalkyl rings; and enantiomers, diastereoisomers, salts, hydrates or solvates thereof] were prepared as *inhibitors* of matrix *metalloproteinases*. For example, II was synthesized starting from (2S)-Hydroxysuccinic acid diisopropyl ester in several steps, which showed *inhibitory* activity against MMP-9, MMP-2, MMP-1 and MMP-12 with IC50 values of <100 nM, <100 nM, >10000 nM, <100 nM, resp. II also showed 57% *inhibition* of IL2-induced peritoneal recruitment of lymphocytes at the dose of 3 mg/kg (vs. 76% *inhibition* by dexamethasone at the dose of 1 mg/kg). In general, I are selective *inhibitors* of MMP-12 and MMP-9 relative to the collagenases and stromelysins. Therefore, I and pharmaceutical compns. thereof are useful in the treatment or prophylaxis of diseases or conditions primarily mediated by MMP-12 and/or MMP-9, especially inflammatory conditions, such as multiple sclerosis and fibrosis.

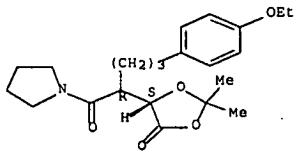
IT *9001-12-1*, MMP-1 *141907-41-7* *146480-35-5*, MMP-2
RL: BSU (Biological study, unclassified); BIOL (Biological study) (inhibitor; preparation of hydroxamates as MMP inhibitors)
RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *847039-01-4P*, (2R)-5-(4-Ethoxyphenyl)-2-((4S)-2,2-dimethyl-5-oxo-[1,3]dioxolan-4-yl)-1-(pyrrolidin-1-yl)pentan-1-one
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of hydroxamates as MMP inhibitors)
RN 847039-01-4 HCAPLUS
CN Pyrrolidine, 1-[(2R)-2-[(4S)-2,2-dimethyl-5-oxo-1,3-dioxolan-4-yl]-5-(4-ethoxyphenyl)-1-oxopentyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT *146480-36-6*, MMP-9
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(selective inhibitor; preparation of hydroxamates as MMP inhibitors)
RN 146480-36-6 HCAPLUS
CN Gelatinase B (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RETABLE

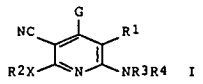
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Chu-Biao, X	1997			US 5703092 A	HCAPLUS
Davies	2003			WO 03070711 A	HCAPLUS
Hoffmann La Roche	1995			EP 0684240 A	HCAPLUS
Jacobs, J	2001			WO 0144179 A1	HCAPLUS
Leo Pharmaceutical Prod	1999			WO 9944989 A1	HCAPLUS
Marie, S	1999			US 5917090 A	HCAPLUS
Versicor Inc Usa	2002			WO 02102791 A1	HCAPLUS

L91 ANSWER 4 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:824492 HCAPLUS Full-text
DOCUMENT NUMBER: 143:222525
TITLE: Method of using 3-cyano-4-arylpyridine derivatives as modulators of androgen receptor function, preparation thereof, and use with other agents
INVENTOR(S): Nirschl, Alexandra A.; Hamann, Lawrence G.

PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 25 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2005182105	A1	20050818	US 2005-48437		20050201 <--
PRIORITY APPLN. INFO.:			US 2004-541780P	P	20040204 <--

OTHER SOURCE(S): MARPAT 143:222525
GI

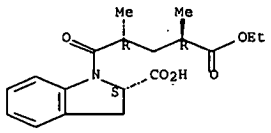


I

AB A method is provided for treating androgen receptor-associated conditions, such as age-related diseases, e.g. sarcopenia, employing a compound I [R1 = CN, H; X = O, S; R2 = (substituted) alkyl, (substituted) cycloalkyl, etc; R3, R4 = H, (substituted) alkyl, etc.; G = (substituted) aryl, (substituted) heteroaryl], or a pharmaceutically acceptable salt or prodrug ester thereof. Preparation of selected I is described. I may be used in combination with other agents.

IT *82924-03-6*, Pentopril
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(cyanoarylpyridine derivative modulators of androgen receptor function, preparation, and use with other agents)
RN 82924-03-6 HCAPLUS
CN 1H-Indole-1-pentanoic acid, 2-carboxy-2,3-dihydro-α,γ-dimethyl-δ-oxo-, α-ethyl ester, (αR,γR,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT *82707-54-8*, Neutral endopeptidase *141907-41-7*, Matrix metalloproteinase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(*inhibitors*; cyanoarylpyridine derivative modulators of androgen

receptor function, preparation, and use with other agents)
RN 82707-54-8 HCAPLUS
CN Neprilysin (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L91 ANSWER 5 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:572597 HCAPLUS Full-text
DOCUMENT NUMBER: 143:97637
TITLE: Preparation of amino acid biarylsulfonamides as *metalloproteinase inhibitors*
INVENTOR(S): Levin, Jeremy Ian; Rush, Thomas Saltmarsh; Lovering, Frank; Hu, Yonghan; Li, Jianchang; Li, Wei; Wu, Jun Jun· Hotchandani, Rajeev; Xiang, Jason Shaoyun; Du, Xuemei; Cole, Derek Cecil; Tam, Steve Yikkai
PATENT ASSIGNEE(S): Wyeth, John, and Brother Ltd., USA
SOURCE: U.S. Pat. Appl. Publ., 119 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005143422	A1	20050630	US 2004-1589	20041201 <--
CA 2548518	A1	20050707	CA 2003-2548518	20031222 <--
WO 2005061477	A1	20050707	WO 2003-US40835	20031222 <--
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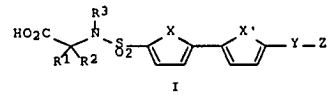
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003299789	A1	20050714	AU 2003-299789	20031222 <--
EP 1692124	A1	20060823	EP 2003-800062	20031222 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003018640	A	20061128	BR 2003-18640	20031222 <--
CN 1623537	A	20050608	CN 2004-10002715	20040105 <--
AU 2004200247	A1	20050623	AU 2004-200247	20040108 <--
NO 2006002649	A	20060901	NO 2006-2649	20060608 <--
PRIORITY APPLN. INFO.:			US 2003-526840P P	20031204 <--
			WO 2003-US40835 W	20031222 <--

GI



I

AB The invention relates to biaryl sulfonamides I [R1, R2 are independently H, CHR4OH, Ph, heteroaryl or alkyl, with the proviso that when R1 or R2 is CHR4OH, then Z is substituted with NR4SO2R5, SO2NR4R5, heterocycloalkyl, heteroaryl or cycloalkyl; R3 is H or alkyl; R4, R5 are independently a bond to the other, H, alkyl or phenyl; X, X' are independently S, O, NR4, CR6:CR6 or N:CR6; R6 is H, halo, an amino group, NO2, CN, etc.; Y is NR3CO, O2C, NHSO2, OCH2, CH2SO or CH2SO2; Z is at least one heteroaryl moiety] and their use as *metalloproteinase inhibitors*. Thus, N-[[4'-[(2-benzofuranylcarbonyl)amino]-1,1'-biphenyl-4- yl]sulfonyl]glycine, prepared by reaction of 4-aminobiphenylsulfonyl fluoride with 2-benzofurancarbonyl chloride and glycine tert-Bu ester hydrochloride and ester cleavage, showed IC50 = 47 nanomolar for *inhibition* of MMP-2.
IT *9001-12-1*, MMP-1 *141256-52-2*, MMP-7 *146480-35-5*, Gelatinase A *146480-36-6*, MMP-9 *161384-17-4*, MMP-14 *175449-82-8*, Collagenase 3
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of amino acid biarylsulfonamides as *metalloproteinase inhibitors*)
RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141256-52-2 HCAPLUS
CN Matrilysin (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

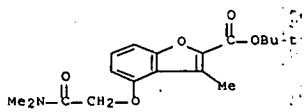
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS
CN Gelatinase B (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 161384-17-4 HCAPLUS
CN Proteinase, matrix metallo-, MT-MMP-1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 175449-82-8 HCAPLUS
CN Collagenase 3 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *857081-89-1P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acid biarylsulfonamides as *metalloproteinase inhibitors*)
RN 857081-89-1 HCAPLUS
CN 2-Benzofurancarboxylic acid, 4-[2-(dimethylamino)-2-oxoethoxy]-3-methyl-,

1,1-dimethylethyl ester (9CI) (CA INDEX NAME)



L91 ANSWER 6 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:387257 HCAPLUS Full-text
DOCUMENT NUMBER: 140:406737
TITLE: Preparation of azabicyclic α7 nicotinic acetylcholine agonists for the treatment of glaucoma and retinal neuropathy
INVENTOR(S): Linn, David Martin; Wong, Erik Ho Fong
PATENT ASSIGNEE(S): Pharmacia & Upjohn Company, USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004039366	A1	20040513	WO 2003-IB4707	20031020 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003269413	A1	20040525	AU 2003-269413	20031020 <--
PRIORITY APPLN. INFO.:			US 2002-423156P P	20021101 <--
			WO 2003-IB4707 W	20031020 <--

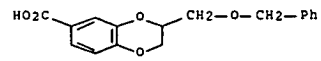
OTHER SOURCE(S): MARPAT 140:406737

AB The invention provides a use or method of treating glaucoma, diabetic retinopathy, or age-related macular degeneration by the administration of azabicycles (azabicyclo-N(R1)C(:X)W (I); X = O, S; R1 = H, alkyl, cycloalkyl, haloalkyl, substituted Ph, substituted naphthyl; W = substituted Ph, (un)substituted 5- or 6-membered heterocyclyl, etc.; addnl. details are given in the claims) that are α7 nAChR agonists (no data) to a mammal in need thereof. Although the methods of preparation are not claimed, many example prepns. of intermediates are included. For example, intermediate exo-(4S)-3-amino-1-azabicyclo[2.2.1]Heptane bis(p-toluenesulfonate) was prepared in 8 steps (68, 62, 76, 100, 77, 94, 46, 84 % yields, resp.) starting with reaction of benzoyl chloride with 2-nitroethanol to give 2-(benzoyloxy)-1-nitroethane, reaction of Et E-4-bromo-2-butenoate with benzylamine to give Et E-4-(benzylamino)-2- butenoate, reaction of these 2 products to give trans-4-

nitro-1- (phenylmethyl)-3-pyrrolidineacetic acid Et ester, reduction to trans-4-amino-1-(phenylmethyl)-3-pyrrolidineacetic acid Et ester, N-protection, reduction to trans-3-(tert-butoxycarbonylamino)-4-(2- hydroxyethyl)-1-(phenylmethyl)pyrrolidine, chromatog. resolution, cyclization of the (+)-enantiomer to give exo-(4S)-3-(tert-butoxycarbonylamino)-1-azabicyclo[2.2.1]heptane and finally deprotection. In another example, N-[(3R)-1-azabicyclo[2.2.2]oct-3-yl]-4-bromo-1H-pyrazole-1-carboxamide hydrochloride was prepared (25 %) by treating 4-bromopyrazole with phosgene followed by (R)-(+)-3-aminoquinuclidine dihydrochloride and excess Et3N, followed by NaOH.

IT *141907-41-7*, Matrix *metalloproteinase*
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors, codrugs; preparation of azabicyclic α7 nicotinic acetylcholine agonists for treatment of glaucoma and retinal neuropathy)
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *527680-80-4P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of azabicyclic α7 nicotinic acetylcholine agonists for treatment of glaucoma and retinal neuropathy)
RN 527680-80-4 HCAPLUS
CN 1,4-Benzodioxin-6-carboxylic acid, 2,3-dihydro-3-[(phenylmethoxy)methyl]- (9CI) (CA INDEX NAME)



L91 ANSWER 7 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:913055 HCAPLUS Full-text
DOCUMENT NUMBER: 139:399770
TITLE: Medical goods comprising heparin or chitosan-based hemocompatible coating
INVENTOR(S): Horres, Roland; Linssen, Marita Katharina; Hoffmann, Michael; Faust, Volker; Hoffmann, Erika; Di Biase, Donato
PATENT ASSIGNEE(S): Hemoteq G.m.b.H., Germany
SOURCE: PCT Int. Appl., 93 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003094990	A1	20031120	WO 2003-DE1253	20030415 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM,				

PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT,
TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY,
KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,
FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR,
BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

DE 10221055	A1	20031127	DE 2002-10221055	20020510 <--
DE 10261986	A1	20040318	DE 2002-10261986	20020510 <--
AU 2003240391	A1	20031111	AU 2003-240391	20030415 <--
CA 2484269	A1	20031120	CA 2003-2484269	20030415 <--
CN 1543362	A	20041103	CN 2003-800770	20030415 <--
EP 1501565	A1	20050202	EP 2003-729829	20030415 <--
EP 1501565	B1	20061102		

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK

BR 2003011446	A	20050315	BR 2003-11446	20030415 <--
US 2005176678	A1	20050811	US 2003-513982	20030415 <--
CN 1665554	A	20050907	CN 2003-815926	20030415 <--
JP 2005534724	T	20051117	JP 2004-503070	20030415 <--
AT 344064	T	20061115	AT 2003-729829	20030415 <--
IN 2004MN00606	A	20050218	IN 2004-MN606	20041028 <--
ZA 2004008791	A	20050527	ZA 2004-8791	20041028 <--
ZA 2004008757	A	20050531	ZA 2004-8757	20041028 <--
PRIORITY APPLN. INFO.:			US 2002-378676P P	20020509 <--
			DE 2002-10221055 A	20020510 <--
			WO 2003-DE1253 W	20030415 <--

AB The invention relates to oligo- and polysaccharides containing the sugar structural element N-acylglucosamine or N-acylgalactosamine, in addition to the use thereof for producing hemocompatible surfaces and to methods for coating surfaces in a hemocompatible manner with said oligo- and polysaccharides, which constitute the common biosynthetic precursor substances of heparin, heparan sulfates and chitosan. The invention also relates to methods for producing the oligo- and/or polysaccharides, in addition to diverse application options involving hemocompatible surfaces. The invention specifically relates to the use of the oligo- and/or polysaccharides on stents involving at least one hemocompatible coating that has been applied according to the invention and that contains an anti-proliferative, anti-inflammatory and/or athrombogenic active ingredient, to methods for producing said stents and to the use of the latter for preventing restenosis. Thus desulfated and reacetylated heparin was prepared; the Ac-heparin product was used for coating coronary metal stents. The stents were implanted in swines; after four weeks the animals were anesthetized and the artery segments removed for histomorphometric anal.

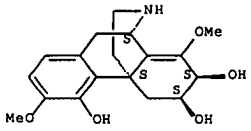
IT *9001-12-1*, Matrix *metalloproteinase*-1
146480-35-5, Matrix *metalloproteinase*-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(*inhibitors* of; medical goods comprising a heparin-based hemocompatible coating)
RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *109351-36-2*, Sinococuline
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(medical goods comprising a heparin-based hemocompatible coating)
RN 109351-36-2 HCAPLUS

CN Morphinan-4,6,7-triol, 8,14-didehydro-3,8-dimethoxy-, (6β,7β,9α,13α)- (9CI) (CA INDEX NAME)

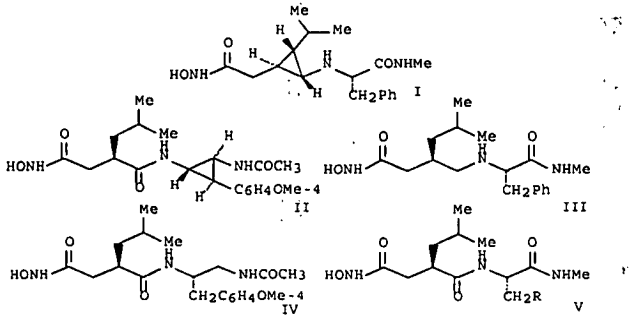
Absolute stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baxter Biotech Technolo	1999			WO 9927976 A	HCAPLUS
Kovanen, P	1999			WO 9926983 A	HCAPLUS

L91 ANSWER 8 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:378120 HCAPLUS Full-text
DOCUMENT NUMBER: 137:109479
TITLE: Design, Synthesis, and Evaluation of Matrix Metalloprotease Inhibitors Bearing Cyclopropane-Derived Peptidomimetics as P1' and P2' Replacements
AUTHOR(S): Reichelt, Andreas; Gaul, Christoph; Frey, Robin R.; Kennedy, April; Martin, Stephen F.
CORPORATE SOURCE: Department of Chemistry and Biochemistry and the Institute for Cellular and Molecular Biology, The University of Texas, Austin, TX, 78712, USA
SOURCE: Journal of Organic Chemistry (*2002*), 67(12), 4062-4075
CODEN: JOCEAH; ISSN: 0022-3263
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:109479
GI



AB Conformationally constrained cyclopropane-based pseudodipeptides I and II and their flexible, linear analogs III and IV were synthesized and evaluated as ***inhibitors*** of matrix ***metalloproteinases*** (MMPs). I and II are analogs of pseudodipeptides V (R = C6H4OMe-4, Ph) that are known to be potent MMP ***inhibitors***. The anti orientations of the iso-Pr side chain in I and the aromatic ring in II relative to the peptide backbone substituents on the cyclopropane were predicted to correspond to the known orientations of the P1' and P2' side chains of V (R = Ph) when bound to MMPs. Hence, I and II were designed explicitly to probe topol. features of the S1' or the S2' binding pockets of the MMPs. They were also designed to explore the importance of the P1'-P2' amide group, which is known to form highly conserved hydrogen bonds in several MMP-***inhibitor*** complexes, and the viability of introducing a retro amide linkage between P2' and P3'. I and III were found to be weak competitive ***inhibitors*** of a series of MMPs. Any entropically favorable conformational constraints that were induced by the cyclopropane in I were thus overwhelmed by the loss of the hydrogen bonding capability associated with the P1'-P2' amide group. On the other hand, II and IV, which contain a P2'-P3' retro amide group, were modest competitive ***inhibitors*** of a series of MMPs, and these results suggest that there may be a loss of hydrogen bonding capability associated with introducing the P2'-P3' retro amide group.

IT ***9001-12-1***, MMP-1 ***79955-99-0***, MMP-3 ***141256-52-2***, MMP 7 ***146480-35-5***, MMP 2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(preparation of cyclopropane-derived pseudodipeptides and their evaluation as matrix metalloprotease inhibitors)

RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 79955-99-0 HCAPLUS
CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141256-52-2 HCAPLUS
CN Matrilysin (CA INDEX NAME)

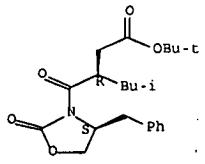
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS

CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT ***144287-83-2P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclopropane-derived pseudodipeptides and their evaluation as matrix metalloprotease inhibitors)

RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Babine, R	1997	97	1359	Chem Rev	HCAPLUS
Baker, W	1992	2	1405	Bioorg Med Chem Lett	HCAPLUS
Basha, A	1977	48	4171	Tetrahedron Lett	
Beckett, R	1993		137	Synlett	HCAPLUS
Bernstein, P	1994	31	59	Prog Med Chem	HCAPLUS
Boger, D	1995	117	12452	J Am Chem Soc	HCAPLUS
Boumendjel, A	1996	61	4434	J Org Chem	HCAPLUS
Bovy, P	1994	2	881	Bioorg Med Chem	HCAPLUS
Bravo, A	1991		3117	J Chem Soc, Perkin T	HCAPLUS
Cannon, J	1975	40	182	J Org Chem	HCAPLUS
Chen, J	1996	6	1601	Bioorg Med Chem Lett	HCAPLUS
Chen, L	1995	36	8715	Tetrahedron Lett	HCAPLUS
Cherney, R	1998	41	1749	J Med Chem	HCAPLUS
Corey, E	1984	25	3559	Tetrahedron Lett	HCAPLUS
Dalcanale, E	1986	51	567	J Org Chem	HCAPLUS
Damon, R	1990	31	2849	Tetrahedron Lett	HCAPLUS
Davidson, J	2002	124	205	J Am Chem Soc	HCAPLUS
Davidson, J	2000	41	9459	Tetrahedron Lett	HCAPLUS
Decicco, C	2001	3	1029	Org Lett	HCAPLUS
Declerck, Y	1994	30A	2170	Eur J Cancer	MEDLINE
Devlin, J	1975		830	J Chem Soc, Perkin T	HCAPLUS
Dickens, J	1986			US 4599361	HCAPLUS
Dickens, J	1988			US 4743587	HCAPLUS
Doyle, M	1991	113	1423	J Am Chem Soc	HCAPLUS
Doyle, M	1995	117	5763	J Am Chem Soc	HCAPLUS
Effenberger, F	1983	22	65	Angew Chem, Int Ed E	
Evans, D	1993	115	4497	J Am Chem Soc	HCAPLUS
Fukuyama, T	1990	112	7050	J Am Chem Soc	HCAPLUS

Fukuyama, T	1995	36	6373	Tetrahedron Lett	HCAPLUS
Fukuyama, T	1997	38	5831	Tetrahedron Lett	HCAPLUS
Gante, J	1994	33	1699	Angew Chem, Int Ed E	
Gassman, P	1976	98	1275	J Am Chem Soc	HCAPLUS
Ghose, A	1995	117	4671	J Am Chem Soc	HCAPLUS
Giannis, A	1993	32	1244	Angew Chem, Int Ed E	
Hagihara, M	1992	114	6568	J Am Chem Soc	HCAPLUS
Hagmann, W	1996	31	231	Annu Rep Med Chem	HCAPLUS
Han, Y	1999	64	1972	J Org Chem	HCAPLUS
Hanessian, S	1997	7	3119	Bioorg Med Chem Lett	HCAPLUS
Hanessian, S	1997	53	12789	Tetrahedron	HCAPLUS
Hillier, M	2001	66	1657	J Org Chem	HCAPLUS
Hogberg, T	1987	52	2033	J Org Chem	
Janetka, J	1997	119	441	J Am Chem Soc	HCAPLUS
Jurczak, J	1998	54	6051	Tetrahedron	HCAPLUS
Kaltenbronn, J	1990	33	838	J Med Chem	HCAPLUS
Kolb, M	1990		171	Synthesis	HCAPLUS
Lee, W	1995	30	23	J Periodont Res	MEDLINE
Levy, D	1998	41	199	J Med Chem	HCAPLUS
Liskamp, R	1994	113	1	Recl Trav Chim Pays-	HCAPLUS
Marcotte, P	2001		3.7.1	Current Protocols in	
Martin, S	1992	35	1710	J Med Chem	HCAPLUS
Martin, S	1998	41	1581	J Med Chem	HCAPLUS
Martin, S	2000	65	1305	J Org Chem	HCAPLUS
Martin, S	1993	49	3521	Tetrahedron	HCAPLUS
Martin, S	1990	31	4731	Tetrahedron Lett	HCAPLUS
Martin, S	1999	40	2887	Tetrahedron Lett	HCAPLUS
Martin, S	1999	40	6721	Tetrahedron Lett	HCAPLUS
Martin-Vila, M	2000	11	3569	Tetrahedron:Asymmetr	HCAPLUS
Melnick, M	1990	31	961	Tetrahedron Lett	HCAPLUS
Nikam, S	1995	36	197	Tetrahedron Lett	HCAPLUS
Ninomiya, K	1974	30	2151	Tetrahedron	HCAPLUS
Paulini, K	1994		549	Liebigs Ann Chem	HCAPLUS
Penning, T	1990	20	307	Synth Commun	HCAPLUS
Pirrung, M	1995	60	8084	J Org Chem	HCAPLUS
Roos, E	1995	60	1733	J Org Chem	HCAPLUS
Rynbrandt, R	1972		1937	Tetrahedron Lett	HCAPLUS
Schneider, J	1995	95	2169	Chem Rev	HCAPLUS
Schwartz, M	1992	29	271	Prog Med Chem	HCAPLUS
Seebach, D	1973	106	2277	Chem Ber	HCAPLUS
Smith, A	1992	114	10672	J Am Chem Soc	HCAPLUS
Smith, A	2000	2	3809	Org Lett	HCAPLUS
Spurlino, J	1994	19	98	Proteins:Struct, Fun	HCAPLUS
Stams, T	1994	1	119	Struct Biol	HCAPLUS
Steinman, D	1998	8	2087	Bioorg Med Chem Lett	HCAPLUS
Still, W	1978	43	2923	J Org Chem	HCAPLUS
Tretyakov, E	2000	56	10075	Tetrahedron	HCAPLUS
Weinstock, J	1961	26	3511	J Org Chem	HCAPLUS
Whittaker, M	1999	99	2735	Chem Rev	HCAPLUS
Woessner, J	1991	5	2145	FASEB J	HCAPLUS

L91 ANSWER 9 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:265252 HCAPLUS Full-text
DOCUMENT NUMBER: 134:295810
TITLE: Synthesis and use of substituted pyrrolidin-1-yl hexanoic acid derivatives as αvβ3 and αvβ5 integrin receptors
INVENTOR(S): Askew, Ben C.; Smith, Garry R.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 141 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001024797	A1	20010412	WO 2000-US27033	20000929 <--
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2386030	A1	20010412	CA 2000-2386030	20000929 <--
EP 1229910	A1	20020814	EP 2000-967201	20000929 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
JP 2003510360	T	20030318	JP 2001-527796	20000929 <--
US 6413955	B1	20020702	US 2000-677677	20001002 <--
PRIORITY APPLN. INFO.:			US 1999-157490P P	19991004 <--
			WO 2000-US27033 W	20000929 <--

OTHER SOURCE(S): MARPAT 134:295810
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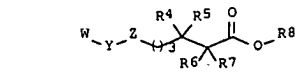

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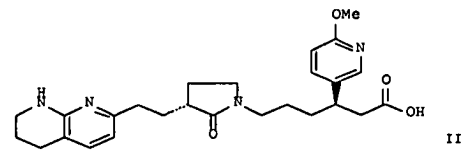


II

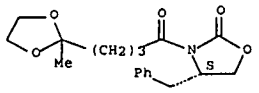
AB Compds. of formula I (wherein; W is a 5 or 6 membered monocyclic (aromatic) ring having 1-4 heteroatoms (N, O or S) wherein the ring nitrogen atoms are unsubstituted or substituted with 1 or 2 R1 groups, or a 9-14 membered polycyclic ring system, wherein the polycyclic ring system has 1-4 heteroatoms (N, O or S) in which the N atoms are substituted as described above; Y is (CH2)m, (CH2)m-(O, NR2 or S(O)0-2)-(CH2)n, etc., where any CH2 can be substituted with 1 or 2 R3 groups, m is 0-3 and n is 0-3; Z is a 5-6 membered heterocyclic system having 1-3 heteroatoms (N, O or S) optionally substituted with one or more R9 group and when 2 R9 substituents are on the same C-atom, they are taken together to form a C3-C6 cycloalkyl group; R1 is H, halo,

(cyclo)alkyl, cycloheteroalkyl, aryl(alkyl), amino(alkyl), etc.; R2 is H, alkyl, aryl(alkyl), aminocarbonyl, cycloalkyl, aminoalkyl, etc.; R3 is H, alkyl, aryl(alkyl), halo, OH, oxo, CF3, etc.; R4 and R5 are H, alkyl, aryl(alkyl), halo, OH, alkylcarbonylamino, etc. or taken together the C-atom to form a CO; R6 and R7 are H, alkyl, aryl(alkyl), halo, OH, etc.; R8 is H, alkyl, aryl(alkyl), alkylcarbonyloxyalkyl, etc.; R9 is H, alkyl, aryl, halo, OH, etc.;]. Several examples of I are provided. For instance II was synthesized in 14 steps as a single enantiomer. Compds. I are antagonists of the integrin receptors αvβ3 and/or αvβ5. Compds. I were found to bind to human αvβ3 integrin with IC50 values less than 10 nM and to the αvβ5 integrin receptor with IC50 values less than 100 nM in competitive binding assays. A bone resorption-pit assay demonstrated the ability of compds. I to inhibit osteoclasts (bovine bone slices). Claimed uses for I are for inhibiting bone resorption, treating and preventing osteoporosis, inhibiting vascular restenosis, diabetic retinopathy, macular degeneration, angiogenesis, atherosclerosis, inflammatory arthritis, cancer, and metastatic tumor growth.

IT *141907-41-7*, Matrix *metalloproteinase*
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(pharmaceuticals also containing *inhibitors* of; preparation and use of substituted pyrrolidin-1-yl hexanoic acid derivs. as αvβ3 and αvβ5 integrin receptor antagonists)
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

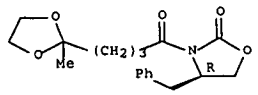
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *334009-77-7P 334009-84-6P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and use of substituted pyrrolidin-1-yl hexanoic acid derivs. as
αvβ3 and αvβ5 integrin receptor antagonists)
RN 334009-77-7 HCAPLUS
CN 2-Oxazolidinone, 3-[4-(2-methyl-1,3-dioxolan-2-yl)-1-oxobutyl]-4-(phenylmethyl)-, (4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 334009-84-6 HCAPLUS
CN 2-Oxazolidinone, 3-[4-(2-methyl-1,3-dioxolan-2-yl)-1-oxobutyl]-4-(phenylmethyl)-, (4R)- (9CI) (CA INDEX NAME)

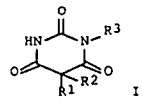
Absolute stereochemistry. Rotation (+).



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Bertson	2000	10	1943	Bioorganic and Medic	

L91 ANSWER 10 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:279024 HCAPLUS Full-text
DOCUMENT NUMBER: 135:92596
TITLE: Novel 5,5-disubstituted pyrimidine-2,4,6-triones as selective MMP inhibitors
AUTHOR(S): Foley, L. H.; Palermo, R.; Dunten, P.; Wang, P.
CORPORATE SOURCE: Roche Research Center, Hoffmann-La Roche Inc., Nutley, NJ, 07110, USA
SOURCE: Bioorganic & Medicinal Chemistry Letters (*2001*), 11(8), 969-972
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 135:92596
GI



I

AB The 5,5-disubstituted pyrimidine-2,4,6-triones I (R1 = H, Me, Et hexyl, HOCH2CH2, PhCH2OCH2; R2 = Ph, 4-PhC6H4, 4-PhOC6H4, 4-octyl-OC6H4; R3 = H, Me) were prepared and shown to be a novel and non-toxic class of matrix *metalloproteinase* (MMP) *inhibitors* showing selectivity for the gelatinases A and B, collagenase-3, and human neutrophil collagenase. The selectivities shown for MMPs-2, -8, -9, and -13 make I very attractive antitumor agents.

IT *146480-35-5*, Gelatinase A *146480-36-6*, Gelatinase B
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of disubstituted pyrimidine triones as selective matrix metalloprotein (MMP) inhibitors)
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS

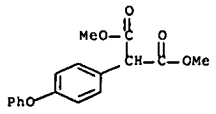
CN Gelatinase B (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *288103-00-4*
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of disubstituted pyrimidine triones as selective matrix metalloprotein (MMP) inhibitors)

RN 288103-00-4 HCAPLUS

CN Propanedioic acid, (4-phenoxyphenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Artis, D	1998	120	12200	J Am Chem Soc	HCAPLUS
Bickett, D	1993	212	58	Anal Biochem	HCAPLUS
Brandstetter, H	2001			J Biol Chem in press	
Dhanaraj, V	1999	72	575	Croatica Chem Acta	HCAPLUS
Dunten, P	2001			Protein Sci in press	
Garbett, E	1999	81	287	Br J Cancer	HCAPLUS
Itoh, T	1998	58	1048	Cancer Res	HCAPLUS
Kjellin, B	1973	27	209	Acta Chem Scand	
Liotta, L	1980	284	67	Nature	HCAPLUS
Marcy, A	1991	30	6476	Biochemistry	HCAPLUS
Murphy, G	1992	283	637	Biochem J	HCAPLUS
Sang, Q	1996	15	243	J Protein Chem	HCAPLUS
Skiles, J	2000	35	167	Annu Rep Med Chem	HCAPLUS
Stetler-Stevenson, W	1993	9	541	Annu Rev Cell Biol	HCAPLUS

L91 ANSWER 11 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:573780 HCAPLUS Full-text
DOCUMENT NUMBER: 133:164063
TITLE: Preparation of pyrimidine-2,4,6-triones as matrix *metalloproteinase inhibitors*
INVENTOR(S): Foley, Louise Helen; Palermo, Robert Edward; Wang, Ping
PATENT ASSIGNEE(S): F. Hoffmann-La Roche A.-G., Switz.
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000047565	A1	20000817	WO 2000-EP1016	20000209 <--

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6265578	B1	20010724	US 2000-483358	20000117 <--
CA 2361605	A1	20000817	CA 2000-2361605	20000209 <--
BR 2000008109	A	20011106	BR 2000-8109	20000209 <--
EP 1153015	A1	20011114	EP 2000-907524	20000209 <--
EP 1153015	B1	20040929		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
TR 200102334	T2	20020121	TR 2001-2334	20000209 <--
JP 2002536439	T	20021029	JP 2000-598486	20000209 <--
JP 3655551	B2	20050602		
AU 774487	B2	20040701	AU 2000-29085	20000209 <--
AT 277912	T	20041015	AT 2000-907524	20000209 <--
PT 1153015	T	20041231	PT 2000-907524	20000209 <--
ES 2226790	T3	20050401	ES 2000-907524	20000209 <--
ZA 2001006214	A	20021028	ZA 2001-6214	20010727 <--

PRIORITY APPLN. INFO.: US 1999-119903P P 19990212 <--
WO 2000-EP1016 W 20000209 <--

OTHER SOURCE(S): MARPAT 133:164063

AB R2CRRCH2R1 (RR = CONHCONHCO) [I; R1 = H, alkyl, alkoxy, aryloxy, etc.; R2 = aryloxyphenyl] were prepared Thus, 4-(PhO)C6H4CH2CO2Me was treated with NaH/(MeO)2CO and the product alkylated with BuCH2CH2I to give 4-(PhO)C6H4C(CH2CH2Bu)(CO2Me)2 which was cyclocondensed with urea to give I [R1 = CH2Bu, R2 = C6H4(OPh)-4]. Data for biol. activity of I were given.

IT *141907-41-7*, Matrix *metalloproteinase*
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated disorders; treatment; preparation of pyrimidine-2,4,6-triones as matrix *metalloproteinase inhibitors*)

RN 141907-41-7 HCAPLUS

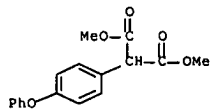
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *288103-00-4P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of pyrimidine-2,4,6-triones as matrix *metalloproteinase inhibitors*)

RN 288103-00-4 HCAPLUS

CN Propanedioic acid, (4-phenoxyphenyl)-, dimethyl ester (9CI) (CA INDEX NAME)



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Boehringer Mannheim G M	1998			WO 9858915 A	HCAPLUS
Boehringer Mannheim G M	1998			WO 9858925 A	HCAPLUS
Boehringer Mannheim Gmb	1997			WO 9723465 A	HCAPLUS

L91 ANSWER 12 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:421569 HCAPLUS Full-text
DOCUMENT NUMBER: 131:68144
TITLE: Angiotensin-converting enzyme *inhibitor* -matrix *metalloproteinase inhibitor* combinations for treatment of fibrosis, ventricular dilation, and heart failure
INVENTOR(S): Peterson, Joseph Thomas, Jr.; Pressler, Milton Lethan
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 156 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9932150	A1	19990701	WO 1998-US23993	19981110 <--
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GE, HR, HU, ID, IL, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2305436	A1	19990701	CA 1998-2305436	19981110 <--
AU 9915220	A	19990712	AU 1999-15220	19981110 <--
AU 751701	B2	20020822		
BR 9814422	A	20001010	BR 1998-14422	19981110 <--
EP 1047450	A1	20001102	EP 1998-959416	19981110 <--
EP 1047450	B1	20021002		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
HU 200100427	A2	20010628	HU 2001-427	19981110 <--
HU 200100427	A3	20021128		
JP 2001526245	T	20011218	JP 2000-525140	19981110 <--
NZ 503962	A	20020328	NZ 1998-503962	19981110 <--
AT 225187	T	20021015	AT 1998-959416	19981110 <--
ES 2184340	T3	20030401	ES 1998-959416	19981110 <--
ZA 9811794	A	19990629	ZA 1998-11794	19981222 <--
US 6133304	A	20001017	US 2000-485253	20000207 <--
MX 200003736	A	20001020	MX 2000-3736	20000417 <--
NO 2000003256	A	20000622	NO 2000-3256	20000622 <--
PRIORITY APPLN. INFO.:			US 1997-68594P P	19971223 <--
			WO 1998-US23993 W	19981110 <--

OTHER SOURCE(S): MARPAT 131:68144

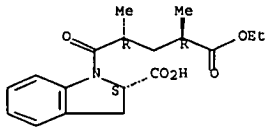
AB Combinations of ACE inhibitors and MMP inhibitors are useful to slow and reverse the process of fibrosis, ventricular dilation, and heart failure in mammals.

IT *82924-03-6*, Pentopril

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(ACE *inhibitor*-matrix *metalloproteinase inhibitor* combinations for treatment of fibrosis, ventricular dilation, and heart failure)

RN 82924-03-6 HCAPLUS
CN 1H-Indole-1-pentanoic acid, 2-carboxy-2,3-dihydro-α,γ-dimethyl-δ-oxo-, α-ethyl ester, (αR,γR,2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



IT *9001-12-1*, Matrix *metalloproteinase* 1 *79955-99-0*, Matrix *metalloproteinase* 3 *141256-52-2*, Matrix *metalloproteinase* 7 *141907-41-7*, Matrix *metalloproteinase 146480-35-5*, Matrix *metalloproteinase* 2 *146480-36-6*, Matrix *metalloproteinase* 9
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(ACE *inhibitor*-matrix *metalloproteinase inhibitor* combinations for treatment of fibrosis, ventricular dilation, and heart failure)

RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 79955-99-0 HCAPLUS
CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141256-52-2 HCAPLUS
CN Matrilysin (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS
CN Gelatinase B (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baxter, A	1997	7	897	Bioorganic & Medicin	HCAPLUS
Li	1998	30	254	J Mol Cell Cardiolog	
O'Brien, P	1998			US 5756545 A	HCAPLUS
Pfizer	1991			WO 9117771 A	HCAPLUS
Searle & Co	1996			WO 9624373 A	HCAPLUS
Warner Lambert Co	1997			WO 9744315 A	HCAPLUS

L91 ANSWER 13 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:733851 HCAPLUS Full-text
DOCUMENT NUMBER: 131:336941
TITLE: Preparation of [(aroylalkyl)amino]succinylhydroxamic acids and analogs as *inhibitors* of matrix *metalloproteinases* and TNFα secretion
INVENTOR(S): Davidsen, Steven K.; Florjancic, Alan S.; Sheppard, George S.; Giesler, Jamie R.; Xu, Lianhong; Guo, Yan; Curtin, Michael L.; Michaelides, Michael R.; Wada, Carol K.; Holms, James H.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: U.S., 67 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5985911	A	19991116	US 1997-992578	19971217 <--
PRIORITY APPLN. INFO.:			US 1997-35781P P	19970107 <--
OTHER SOURCE(S):	MARPAT 131:336941			

AB RCOCR1R2CHR3CONHCR4R5C(:X)R6 [I; R = NHOH or OH; R1,R4 = H or alkyl; R2 = H, OH, alk(en)yl, alkoxy, etc.; R3 = alk(en)yl, phenyl(alkyl), etc.; R5 = alkyl, Ph, etc.; R6 = alkyl, Ph, heteroaryl, etc.; X = O or NOR1] were prepared Thus, indole was acylated by L-MeO2CNHCH(CH2Ph)CO2H and the N-deprotected product amidated by (S,S)-RCOCHR2CHR3COR7 (R2 = CH2CH:CH2, R3 = CH2Ph)(II; R = OCMe3, R7 = OC6F5) to give II [R7 = NHCH(CH2Ph)COR6, R6 = 3-indolyl](III; R = OCMe3) which was converted in 2 steps to III (R = NHOH). Data for biol. activity of I were given.

IT *141907-41-7*, Matrix *metalloproteinase*
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated disorders; treatment; preparation of [(aroylalkyl)amino]succinylhy droxamic acids and analogs as *inhibitors* of matrix *metalloproteinases* and TNFα secretion)

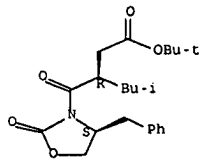
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of [(aroylalkyl)amino]succinylhydroxamic acids and analogs as *inhibitors* of matrix *metalloproteinases* and TNFα secretion)

RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1991			WO 9102716	HCAPLUS
Anon	1992			EP 0489577	HCAPLUS
Anon	1992			EP 0498665	HCAPLUS
Anon	1992			WO 9213831	HCAPLUS
Anon	1993			EP 0575844	HCAPLUS
Anon	1993			WO 9324449	HCAPLUS
Anon	1994			WO 9402446	HCAPLUS
Anon	1994			WO 9402447	HCAPLUS
Anon	1994			WO 9410990	HCAPLUS
Anon	1994			WO 9421612	HCAPLUS
Anon	1994			WO 9422309	HCAPLUS
Anon	1994			WO 9424140	HCAPLUS
Anon	1994			WO 9425435	HCAPLUS
Anon	1995			WO 9504735	HCAPLUS
Anon	1995			WO 9506031	HCAPLUS
Anon	1995			WO 9519956	HCAPLUS
Anon	1995			WO 9519961	HCAPLUS
Anon	1995			WO 9522966	HCAPLUS
Anon	1995			WO 9523790	HCAPLUS
Anon	1995			WO 9529892	HCAPLUS
Anon	1995			WO 9532944	HCAPLUS
Anon	1996			WO 9616027	HCAPLUS
Anon	1996			WO 9616931	HCAPLUS
Anon	1996			WO 9633161	HCAPLUS
Anon	1997			WO 9718207	HCAPLUS
Anon	1994	370	218	Nature	
Anon	1994	370	555	Nature	
Anon	1994	370	558	Nature	
Brown, K				Addn to Brit 1,206,4	
Goldsmith	1972	9	32	Proc Soc Anal Chem	HCAPLUS
Handa	1991			US 4996358	HCAPLUS
Ibrahim, F	1995	18	2621	J Liq Chromatogr	HCAPLUS
Isomura	1995			US 5442110	HCAPLUS
Porter	1994			US 5300501	HCAPLUS
Short, F	1969	6	707	J Heterocycl Chem	HCAPLUS

L91 ANSWER 14 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:582646 HCAPLUS Full-text
DOCUMENT NUMBER: 131:214555
TITLE: Preparation of macrocyclic peptide *inhibitors* of matrix *metalloproteinases* and TNFα secretion
INVENTOR(S): Davidsen, Steven K.; Steinman, Douglas H.; Sheppard, George S.; Xu, Lianhong; Holms, James H.; Guo, Yan; Summers, James B.; Florjancic, Alan S.; Michaelides, Michael R.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: U.S., 82 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5952320	A	19990914	US 1997-992668	19971217 <--
PRIORITY APPLN. INFO.:			US 1997-35780P	P 19970107 <--

OTHER SOURCE(S): MARPAT 131:214555
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Macrocyclic compds. I [W = NHOH, OH; R1, R3 = H, alkyl; R2 = (un)substituted alkyl, cycloalkyl, Ph, phenylalkyl, etc.; Y is absent or O; L1 = alkylene; L2 = (un)substituted Ph or pyridyl; A is ab sent or O, NH or imino group, S, SO, SO2, S2, CH:CH, CO, etc.; Z is an acyl group] were prepared as *inhibitors* of matrix *metalloproteinase* and TNFα secretion. Thus, compound II was prepared via reactions of (2S,3R)-2-allyl-3-isobutylsuccinic acid 1-tert-Bu ester, L-tyrosine benzyl ester tosylate, and 4-(2-aminoethyl)benzenesulfonamide.

IT *81669-70-7, Metalloproteinase*
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of macrocyclic peptide *inhibitors* of matrix *metalloproteinases* and TNFα secretion)

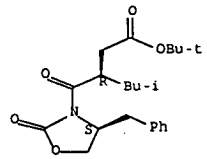
RN 81669-70-7 HCAPLUS
CN Proteinase, metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of macrocyclic peptide *inhibitors* of matrix *metalloproteinases* and TNFα secretion)

RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RETABLE

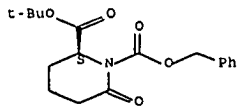
Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1991			WO 9102716	HCAPLUS
Anon	1992			EP 0489577	HCAPLUS
Anon	1992			EP 0498665	HCAPLUS
Anon	1992			WO 9213831	HCAPLUS
Anon	1993			EP 0575844	HCAPLUS
Anon	1993			WO 9324449	HCAPLUS
Anon	1994			WO 9402446	HCAPLUS
Anon	1994			WO 9402447	HCAPLUS
Anon	1994			WO 9410990	HCAPLUS
Anon	1994			WO 9421612	HCAPLUS
Anon	1994			WO 9422309	HCAPLUS
Anon	1994			WO 9424140	HCAPLUS
Anon	1994			WO 9425434	HCAPLUS
Anon	1995			WO 9504735	HCAPLUS
Anon	1995			WO 9506031	HCAPLUS
Anon	1995			WO 9519956	HCAPLUS
Anon	1995			WO 9519961	HCAPLUS
Anon	1995			WO 9522966	HCAPLUS
Anon	1995			WO 9523790	HCAPLUS
Anon	1995			WO 9529892	HCAPLUS
Anon	1995			WO 9532944	HCAPLUS
Anon	1996			WO 9616027	HCAPLUS
Anon	1996			WO 9616931	HCAPLUS
Anon	1996			WO 9633161	HCAPLUS
Anon	1997			WO 9718207	HCAPLUS
Anon	1994	370	218	Nature	
Anon	1994	370	555	Nature	
Anon	1994	370	558	Nature	
Brown, K	1974		4	Brit	
CAS	1997			WO 97/18207	HCAPLUS
Handa	1991			US 4996358	HCAPLUS
Ibrahim, F	1995	18	2621	J Liq Chromatogr	HCAPLUS
Isomura	1995			US 5442110	HCAPLUS
Porter	1994			US 5300501	HCAPLUS
Short, F	1969	6	707	J Heterocycl Chem	HCAPLUS
Wyeth, J	1972	9	32	Proc Soc Anal Chem	

L91 ANSWER 15 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:2287 HCAPLUS Full-text
DOCUMENT NUMBER: 132:322101
TITLE: Synthesis of a new dual metalloprotease inhibitor. I. Diastereoselective alkylation of protected 6-oxopipecolic acid esters. [Erratum to document cited

in CA132:180836)
AUTHOR(S): Akasaka, Kozo; Akamatsu, Hiroshi; Kimoto, Yuichi; Komatsu, Yuki; Kotake, Makoto; Shimizu, Toshikazu; Shimomura, Naoyuki; Tagami, Katsuya; Negi, Shigeto
CORPORATE SOURCE: Tsukuba Research Laboratories, Eisai Co., Ltd., Tsukuba, 300-2635, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (*1999*), 47(12), 1808
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The name of author Makoto Kotake was added with affiliation a.
IT *81669-70-7*, Metalloprotease
RL: MSC (Miscellaneous)
(preparation of N-protected methyloxopipecolate derivs. as synthetic intermediates for dual inhibitors of metalloproteases (Erratum))
RN 81669-70-7 HCAPLUS
CN Proteinase, metallo- (CA INDEX NAME)

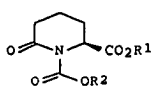
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *259181-45-8P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(study of diastereoselective methylation of N-protected 6-oxopipecolic acid esters (Erratum))
RN 259181-45-8 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 6-oxo-, 2-(1,1-dimethylethyl) 1-(phenylmethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 16 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:765866 HCAPLUS Full-text
DOCUMENT NUMBER: 132:180836
TITLE: Synthesis of a new dual metalloprotease inhibitor. I. Diastereoselective alkylation of protected 6-oxopipecolic acid esters
AUTHOR(S): Akasaka, Kozo; Akamatsu, Hiroshi; Kimoto, Yuichi; Komatsu, Yuki; Shimizu, Toshikazu; Shimomura, Naoyuki; Tagami, Katsuya; Negi, Shigeto
CORPORATE SOURCE: Tsukuba Research Laboratories, Eisai Co., Ltd., Tsukuba, 300-2635, Japan
SOURCE: Chemical & Pharmaceutical Bulletin (*1999*), 47(11), 1525-1531
CODEN: CPBTAL; ISSN: 0009-2363
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 132:180836
GI



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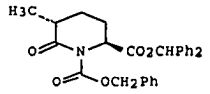
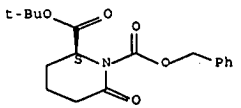


II

AB Diastereoselective methylation of the enolate generated from various protected 6-oxopipecolic acid esters I (R1 = CMe3, CH2Ph, CHPh2; R2 = CH2Ph, Me, CMe3, Ph) was studied. The protecting groups on the carboxylic acid and amino groups significantly influenced the trans/cis selectivity in the methylation reaction. The optimal substrate was diphenylmethyl (2S)-N-benzyloxycarbonyl-6-oxopipecolate I (R1 = CHPh2; R2 = CH2Ph), which gave the 5-methylated product with a trans/cis isomer ratio of ca. 4:1. Investigation of the reaction conditions revealed that the reaction solvent, alkylating reagent, and base employed to generate the enolate, were decisive factors for diastereoselectivity. Further optimization of reaction conditions, including the amts. of the reagents and their addition sequence enabled maximization of reaction conversion and minimization of byproducts to produce the trans-rich diphenylmethyl (2S,trans)-N- benzyloxycarbonyl-5-methyl-6-oxopipecolate (II) on a large scale.
IT *81669-70-7*, Metalloprotease
RL: MSC (Miscellaneous)
(preparation of N-protected methyloxopipecolate derivs. as synthetic intermediates for dual inhibitors of metalloproteases)
RN 81669-70-7 HCAPLUS
CN Proteinase, metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *259181-45-8P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(study of diastereoselective methylation of N-protected 6-oxopipecolic acid esters)
RN 259181-45-8 HCAPLUS
CN 1,2-Piperidinedicarboxylic acid, 6-oxo-, 2-(1,1-dimethylethyl) 1-(phenylmethyl) ester, (2S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



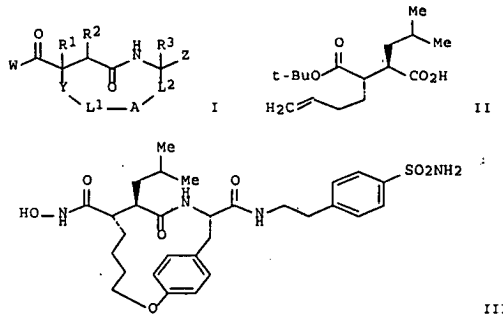
RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Baldwin, J	1989	45	7459	Tetrahedron	HCAPLUS
Ezquerra, J	1993	49	8665	Tetrahedron	HCAPLUS
Murray, P	1996	37	1875	Tetrahedron Lett	HCAPLUS
Robl, J	1994	4	2055	Bioorg & Med Chem Le	
Robl, J	1997	40	1570	J Med Chem	HCAPLUS
Szirtes, T	1986	29	1654	J Med Chem	HCAPLUS

L91 ANSWER 17 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:490632 HCAPLUS Full-text
DOCUMENT NUMBER: 129:136496
TITLE: Preparation of cyclized peptide derivatives as macrocyclic *inhibitors* of matrix *metalloproteinases* and tumor necrosis factor α secretion
INVENTOR(S): Davidsen, Steven K.; Steinman, Douglas H.; Sheppard, George S.; Xu, Lianhong; Holms, James H.; Guo, Yan; Florjancic, Alan Scott; Siummers, James B.; Michaelides, Michael R.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 145 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9830551	A1	19980716	WO 1998-US144	19980107 <--
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
ZA 9800020	A	19980702	ZA 1998-20	19980102 <--
CA 2277121	A1	19980716	CA 1998-2277121	19980107 <--
AU 9858155	A	19980803	AU 1998-58155	19980107 <--
EP 1021423	A1	20000726	EP 1998-901696	19980107 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001509151	T	20010710	JP 1998-531031	19980107 <--
MX 9906338	A	20000131	MX 1999-6338	19990706 <--
PRIORITY APPLN. INFO.:			US 1997-782061 A	19970107 <--
			WO 1998-US144 W	19980107 <--

OTHER SOURCE(S): MARPAT 129:136496
GI



I II III

AB Cyclized peptide derivs. I [W = NHOH, OH; R1, R3 = independently H, C1-4 alkyl; R2 = C1-10 alkyl, C2-10 alkenyl, C3-8 cycloalkyl, C1-6 alkyl-C3-8 cycloalkyl, C5-8 cycloalkylene, C1-6 alkyl-C5-8 cycloalkylene, (un)substituted Ph, (un)substituted C1-6 alkyl-Ph, (CH2)mT(CH2)nR6, C1-4 alkyl-fluorenyl; n, m = independently 0-4; T = O, S; R6 = C1-4 alkyl, (un)substituted phenyl; Y = bond, O; L1 = C2-6 alkylene; L2 = C1-6 alkylene, (un)substituted C0-4 alkyl-phenylene, (un)substituted C0-4 alkyl-pyridinediyl; A = bond, O, NR9, S(O)q, SS, CH:CH, etc; R9 = H, C1-4 alkyl, CO2R10, CONR7R8, COR10, SO2R10; R7, R8 = independently H, C1-4 alkyl; NR7R8 = 5-6-membered heterocyclic ring; R10 = C1-4 alkyl, (un)substituted Ph, C1-4 alkyl-(un)substituted Ph, C1-4 alkyl-heteroaryl; q = 0-2; Z = absent, CO2H, CO2R10, CONR13R14; R13 = H, C1-6 alkyl; R14 = H, C1-6 alkyl, C3-8 cycloalkyl, C1-4 alkyl-C3-8 cycloalkyl, C5-8 cycloalkenyl, C1-4 alkyl-C5-8 cycloalkenyl, SO2R10, etc.] are potent *inhibitors* of matrix *metalloproteinase* and are useful in the treatment of diseases in which matrix *metalloproteinase* play a role. Also disclosed are matrix *metalloproteinase inhibiting* compns. and a method of *inhibiting* matrix *metalloproteinase* in a mammal. Thus, peptide coupling of succinate ester II (preparation given) with H-Tyr-OCH2Ph.HCl, followed by hydroboration of the double bond, Mitsunobu ring closure, and selective deprotection and amidation reactions gave desired macrocycle III. III *inhibited* stromelysin with IC50 = 6.9 nM in and in vitro assay.

IT *79955-99-0*, Stromelysin
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of cyclized peptide derivs. as macrocyclic *inhibitors* of matrix *metalloproteinases* and tumor necrosis factor α secretion)
RN 79955-99-0 HCAPLUS
CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *141907-41-7*, Matrix *metalloproteinase*
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of cyclized peptide derivs. as macrocyclic *inhibitors* of matrix *metalloproteinases* and tumor necrosis factor α secretion)
RN 141907-41-7 HCAPLUS

CN Proteinase, matrix metallo- (CA INDEX NAME)

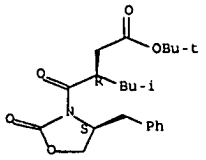
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclized peptide derivs. as macrocyclic *inhibitors* of matrix *metalloproteinases* and tumor necrosis factor α secretion)

RN 144287-83-2 HCAPLUS

CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
British Bio-Technology	1992			WO 9213831 A	HCAPLUS
The Du Pont Merck Pharm	1997			WO 9718207 A	HCAPLUS

L91 ANSWER 18 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:490622 HCAPLUS Full-text
DOCUMENT NUMBER: 129:149247
TITLE: C-terminal ketone hydroxamic acid *inhibitors* of matrix *metalloproteinases* and TNFA secretion
INVENTOR(S): Davidsen, Steven K.; Florjancic, Alan Scott; Sheppard, George S.; Giesler, Jamie R.; Xu, Lianhong; Guo, Yan; Curtin, Michael L.; Michaelides, Michael R.; Wada, Carol K.; Holms, James H.
PATENT ASSIGNEE(S): Abbott Laboratories, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9830541	A1	19980716	WO 1998-US142	19980107 <--

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NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI,
FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM,
GA, GN, ML, MR, NE, SN, TD, TG

ZA 9800018	A	19980702	ZA 1998-1[illegible]		19980102 <--
TW 399042	B	20000721	TW 1998-87100087		19980105 <--
CA 2277105	A1	19980716	CA 1998-2277105		19980107 <--
AU 9859582	A	19980803	AU 1998-59582		19980107 <--
EP 964851	A1	19991222	EP 1998-902771		19980107 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI					
JP 2002503216	T	20020129	JP 1998-531030		19980107 <--
MX 9906337	A	20000131	MX 1999-6337		19990706 <--
PRIORITY APPLN. INFO.:			US 1997-779778	A	19970107 <--
			WO 1998-US142	W	19980107 <--

OTHER SOURCE(S): MARPAT 129:149247
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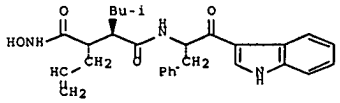


I

AB Amino acid derivs. WCOCR1R2CHR3CONHCR4R5C(:V)R6 [W = NHOH, OH; R1, R4 = H, alkyl; V = O, NOR1; R2 = H, OH, alkoxy, (un)substituted alkyl or alkenyl; R3 = (un)substituted alkyl, Ph, or phenylalkyl, cycloalkyl, cycloalkylalkyl, cycloalkylene, cycloalkylenealkyl; R5 = (un)substituted alkyl or phenyl; R6 = (un)substituted alkyl, Ph, 1,3-benzodioxole, indolyl, pyrrolyl, imidazolyl, benzimidazolyl, pyridyl, thienyl, thiazolyl, oxazolyl, furyl, benzofuryl, benzothiazolyl] were prepared as potent *inhibitors* of matrix *metalloproteinase*. Thus, C-terminal ketone hydroxamic acid I, prepared via reaction of N-carbomethoxy-L-phenylalanine with indole and a disubstituted succinate diester, showed IC50 = 2.3 nM for *inhibition* of stromelysin.

IT *79955-99-0*, Stromelysin *141907-41-7*, Matrix *metalloproteinase*
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(C-terminal ketone hydroxamic acid *inhibitors* of matrix *metalloproteinases* and TNFA secretion)

RN 79955-99-0 HCAPLUS

CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 141907-41-7 HCAPLUS

CN Proteinase, matrix metallo- (CA INDEX NAME)

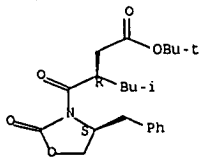
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(C-terminal ketone hydroxamic acid *inhibitors* of matrix *metalloproteinases* and TNFA secretion)

RN 144287-83-2 HCAPLUS

CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

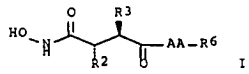
Absolute stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
British Bio-Technology	1992			EP 0498665 A	HCAPLUS
British Biotech Pharmac	1995			WO 9519956 A	HCAPLUS
British Biotech Pharmac	1995			WO 9519961 A	HCAPLUS
British Biotech Pharmac	1995			WO 9532944 A	HCAPLUS
British Biotech Pharmac	1996			WO 9633161 A	HCAPLUS
Celltech Ltd	1992			EP 0489577 A	HCAPLUS
Celltech Ltd	1993			WO 9324449 A	HCAPLUS
Celltech Ltd	1994			US 5300501 A	HCAPLUS
Celltech Ltd	1994			WO 9425435 A	HCAPLUS
F Hoffmann-La Roche Ag	1993			EP 0575844 A	HCAPLUS
Immunex Corp	1995			WO 9506031 A	HCAPLUS

L91 ANSWER 19 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:9156 HCAPLUS Full-text
DOCUMENT NUMBER: 128:84037
TITLE: Matrix *Metalloproteinase Inhibitors* : A Structure Activity Study
AUTHOR(S): Levy, Daniel E.; Lapierre, France; Liang, Weisheng; Ye, Wenqing; Lange, Christopher W.; Li, Xiaoyuan; Grobelny, Damian; Casabonne, Marie; Tyrrell, David; Holme, Kevin; Nadzan, Alex; Galardy, Richard E.
CORPORATE SOURCE: Departments of Chemistry and Biochemistry, Glycomed Inc., Alameda, CA, 94501, USA
SOURCE: Journal of Medicinal Chemistry (*1998*), 41(2), 199-223
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Modifications around the dipeptide-mimetic core of hydroxamic acid based matrix *metalloproteinase inhibitors* I [AA = L-Trp, D-Trp, L-Trp(Me), L-3-benzothienylalanine, L-1- and -2-naphthylalanine, L-3- and -8-quinolylalanine, L-4-phenylphenylalanine, L-Phe, L-3- and -4-pyridylalanine, L-tert-leucine, L-abrine; R6 = NHMe, NH(CH2)4Me, NHCH2CH2OH, NHCH2CH2NHCO2CH2Ph, cyclopropylamino, cyclopentylamino, (S)- and (R)-1-indanylamino, (1R,2S)- and (1S,2R)-2-hydroxy-1-indanylamino, (S)-NHCHMePh, NHCH2Ph, piperonylamino, 2-, 3-, and 4-pyridylmethylamino, 2-(4-pyridyl)ethylamino, NHCH2CH2C6H4OH-4, 2-furanylmethylamino, 2-thiazolylmethylamino, 2-benzimidazolylamino, 3-(1-imidazolyl)propylamino, 3-(4-morpholinyl)propylamino; R2 = H, OH; R3 = CH2CHMe2, Bu, n-hexyl, n-octyl, OCHMe2, O(CH2)4Me] were studied. These variations incorporated a variety of natural, unnatural, and synthetic amino acids in addition to modifications of the P1' and P3' substituents. The results of this study indicate the following structural requirements: (1) Two key hydrogen bonds must be present between the enzyme and potent substrates. (2) Potent *inhibitors* must possess potent zinc-binding functionalities. (3) The potential importance of the hydrophobic group at position R3 as illustrated by its ability to impart greater relative potency against stromelysin when larger hydrophobic groups are used. (4) Requirements surrounding the nature of the amino acid appear to be more restrictive for stromelysin than for neutrophil collagenase, 72 kDa gelatinase, and 92 kDa gelatinase. These requirements may involve planar fused-ring aryl systems and possibly hydrogen-bonding capabilities.

IT *9001-12-1*, Collagenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Neutrophil; preparation and structure-activity of hydroxamic acid-based matrix *metalloproteinase inhibitors*)

RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *79955-99-0*, Stromelysin *141907-41-7*, Matrix *metalloproteinase 146480-35-5*, Gelatinase A *146480-36-6*, Gelatinase B
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation and structure-activity of hydroxamic acid-based matrix *metalloproteinase inhibitors*)

RN 79955-99-0 HCAPLUS
CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

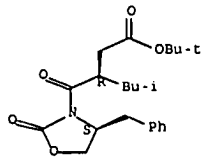
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

RN 146480-36-6 HCAPLUS
CN Gelatinase B (CA INDEX NAME)

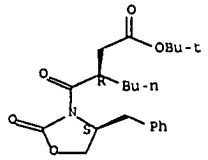
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT ***144287-83-2P 200866-59-7P***
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and structure-activity of hydroxamic acid-based matrix ***metalloproteinase inhibitors***)
RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 200866-59-7 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-butyl-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Acosta, C	1991		110	J Chem Res Synop	HCAPLUS
Ahrens, D	1996	39	1576	Arthritis Rheumatism	MEDLINE
Becker, J	1995	4	1966	Protein Sci	HCAPLUS
Blaser, J	1996	244	17	Clin Chim Acta	MEDLINE
Borkakoti, N	1994	1	106	Struct Biol	HCAPLUS
Buisson, A	1996	166	413	J Cell Physiol	HCAPLUS
Buisson, A	1996	74	658	Lab Invest	HCAPLUS
Caldwell, C	1996	6	323	Bioorg Med Chem Lett	HCAPLUS

Castelhano, A	1995	5	1415	Bioorg Med Chem Lett	HCAPLUS
Chander, S	1995	84	404	J Pharm Sci	HCAPLUS
Chandler, S	1995	201	223	Neurosci Lett	HCAPLUS
Chapman, K	1996	6	329	Bioorg Med Chem Lett	HCAPLUS
Chapman, K	1996	6	803	Bioorg Med Chem Lett	HCAPLUS
Chen, J	1996	6	1601	Bioorg Med Chem Lett	HCAPLUS
Daumas, P	1991	38	218	Int J Pept Protein R	HCAPLUS
Dhanaraj, V	1996	4	375	Structure	HCAPLUS
Dhanaraj, V	1996	4	375	Structure	HCAPLUS
Dugger, R	1992	33	6763	Tetrahedron Lett	HCAPLUS
Esser, C	1997	40	1026	J Med Chem	HCAPLUS
Evans, D	1982	104	1737	J Am Chem Soc	HCAPLUS
Evans, D	1990	112	8215	J Am Chem Soc	HCAPLUS
Fini, M	1996	149	1287	Am J Path	HCAPLUS
Fitzi, R	1988	44	5277	Tetrahedron	HCAPLUS
Foley, M	1996	6	1905	Bioorg Med Chem Lett	HCAPLUS
Folkman, J	1992	267	10931	J Biol Chem	HCAPLUS
Galardy, R	1994	732	315	Ann N Y Acad Sci	HCAPLUS
Galardy, R	1993	18	1109	Drugs Future	
Gowravaram, M	1995	38	2570	J Med Chem	HCAPLUS
Grams, F	1995	34	14012	Biochemistry	HCAPLUS
Hewson, A	1995	44	345	Inflamm Res	HCAPLUS
Holleran, W	1997	289	138	Arch Dermatol Res	HCAPLUS
Hughes, I	1995	5	3039	Bioorg Med Chem Lett	HCAPLUS
Irako, N	1995	51	12731	Tetrahedron	HCAPLUS
Jiracek, J	1996	271	19606	J Biol Chem	HCAPLUS
Knight, C	1992	296	263	Fed Eur Biochem Soc	HCAPLUS
Krippner, G	1994	5	1793	Tetrahedron:Asymmetr	HCAPLUS
Lafleur, M	1996	184	2311	J Exp Med	HCAPLUS
Lawson, W	1968	349	251	Z Physiol Chem	HCAPLUS
Levy, D	1994	29	215	Annu Rep Med Chem	HCAPLUS
Levy, D	1997	2	205	Emerging Drugs:The P	HCAPLUS
Levy, D	1994	4	547	Med Chem Res	HCAPLUS
Maeda, A	1996	55	300	J Neuropathol Exp Ne	MEDLINE
Miller, A	1996			Highland Meeting in	
Morphy, J	1995	2	743	Curr Med Chem	HCAPLUS
Norman, B	1992	33	6803	Tetrahedron Lett	HCAPLUS
Ohishi, K	1995	13	287	Clin Exp Metastasis	HCAPLUS
Saarialhokere, U	1996	148	519	Am J Path	MEDLINE
Sahoo, S	1995	5	2441	Bioorg Med Chem Lett	HCAPLUS
Singh, J	1988		864	Proceedings of the 1	
Stams, T	1994	1	119	Struct Biol	HCAPLUS
Tamaki, K	1995	43	1883	Chem Pharm Bull	HCAPLUS
van Doren, S	1995	4	2487	Protein Sci	HCAPLUS
Weckroth, M	1996	106	1119	J Invest Dermatol	HCAPLUS
Witty, J	1996	11	72	J Bone Mineral Res	HCAPLUS
Zucker, S	1994	732	248	Ann N Y Acad Sci	HCAPLUS

L91 ANSWER 20 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:328697 HCAPLUS Full-text
DOCUMENT NUMBER: 127:44442
TITLE: Synthesis and biological evaluation of orally active matrix ***metalloproteinase inhibitors***
AUTHOR(S): Hirayama, Ryoichi; Yamamoto, Minoru; Tsukida, Takahiro; Matsuo, Konomi; Obata, Yuji; Sakamoto, Fumio; Ikeda, Shoji
CORPORATE SOURCE: Product R&D Laboratory, Kanebo, Ltd., Osaka, 534, Japan
SOURCE: Bioorganic & Medicinal Chemistry (*1997*), 5(4), 765-778

CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The synthesis and biol. evaluation of orally active *inhibitors* of matrix *metalloproteinase* are reported. Modifications of the P2' position and the α-substituent of hydroxamic acid derivs. were carried out, and revealed that the P2' substituent influenced the MMP *inhibitory* activities in vitro and in plasma after oral administration. The hydroxamates with phenylglycine at the P2' position were absorbed well orally. NONHCOCH(Me)CH(CH2CHMe2)CONHCH(Ph)CONHMe, which exhibited the longest duration of *inhibitory* activity in plasma after oral administration among the phenylglycine derivs., was evaluated in a rat adjuvant arthritis model. A reduction in hind foot pad swelling and improvements of some inflammatory parameters were demonstrated when the compound was administered orally. These results indicate the potential of MMP *inhibitors* for rheumatoid arthritis.

IT *9001-12-1*, Matrix *metalloproteinase* 1
146480-36-6, Matrix *metalloproteinase* 9
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(matrix *metalloproteinase inhibitor* preparation and biol. evaluation)

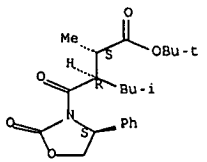
RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-36-6 HCAPLUS
CN Gelatinase B (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *190908-96-4*
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction; matrix *metalloproteinase inhibitor* preparation and biol. evaluation)

RN 190908-96-4 HCAPLUS
CN 3-Oxazolidinebutanoic acid, α-methyl-β-(2-methylpropyl)-γ,2-dioxo-4-phenyl-, 1,1-dimethylethyl ester, [4S-[3(αR*,βS*),4R*]]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RETABLE

Referenced Author (RAU)	Year (RPY)	VOL (RVL)	PG (RPG)	Referenced Work (RWK)	Referenced File
Anon	1991			JP 03-103178	HCAPLUS
Anon	1994			JP 06-86672	

Beckett, R	1996	1	16	Drug Discovery Today	HCAPLUS
British Bio-Technology	1990			WO 9005716	HCAPLUS
Brown, P	1993	2	617	Curr Opin Invest Dru	
Conradi, R	1992	9	435	Pharm Res	HCAPLUS
Conway, J	1995	182	449	J Exp Med	HCAPLUS
Decicco, C	1995	60	4782	J Org Chem	HCAPLUS
Dimartino, R	1994	732	411	Ann N Y Acad Sci	
Docherty, A	1990	49	469	Ann Rheum Dis	MEDLINE
Greenwald, R	1994	732		Ann N Y Acad Sci	HCAPLUS
Henderson, B	1990	15	495	Drugs of the Future	
Inaba, T	1992	65	2539	Bull Chem Soc Jpn	
Johnson, W	1987	2	1	J Enzyme Inhibition	HCAPLUS
Kanebo Ltd	1994			JP 06-145148	HCAPLUS
Kanebo Ltd	1995			JP 07-75571	HCAPLUS
Macachren, S	1991	34	1085	Arthritis Rheum	
Mohler, K	1994	370	218	Nature	HCAPLUS
Nagai, N	1984	4	123	Jpn J Inflamm	
Schwartz, M	1992	29	271	Prog Med Chem	HCAPLUS
Spurlino, J	1994	19	98	Proteins:Struct Func	HCAPLUS
Wahl, R	1995	5	349	Bioorg Med Chem Lett	HCAPLUS

L91 ANSWER 21 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:546363 HCAPLUS Full-text
DOCUMENT NUMBER: 125:189378
TITLE: Hydroxamic acid-containing inhibitors of matrix metalloproteases and their use in pharmaceuticals
INVENTOR(S): Yelm, Kenneth Edward
PATENT ASSIGNEE(S): Procter and Gamble Company, USA
SOURCE: PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9620918	A1	19960711	WO 1995-US16140	19951213 <--
W: AL, AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5639746	A	19970617	US 1994-366062	19941229 <--
CA 2208679	A1	19960711	CA 1995-2208679	19951213 <--
AU 9644220	A	19960724	AU 1996-44220	19951213 <--
AU 706409	B2	19990617		
BR 9510175	A	19971014	BR 1995-10175	19951213 <--
EP 800510	A1	19971015	EP 1995-943083	19951213 <--
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
CN 1171780	A	19980128	CN 1995-197203	19951213 <--
JP 10512241	T	19981124	JP 1995-521011	19951213 <--
NO 9703035	A	19970829	NO 1997-3035	19970627 <--

PRIORITY APPLN. INFO.: US 1994-366062 A 19941229 <--
WO 1995-US16140 W 19951213 <--

OTHER SOURCE(S): MARPAT 125:189378

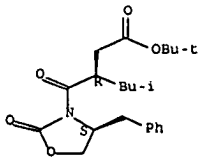
AB The invention provides hydroxamic acid-containing compds. which are useful as inhibitors of matrix metalloproteases and which are effective in treating

conditions associated with excess activity of these enzymes. In particular, the present invention relates to a compound having structure HONHCOCHR1NR2COCHR3CHR4COR5 (R1-5 are independently selected from various substituents; or R3 and R4 or R4 and R5 may together comprise a cyclic moiety) or a pharmaceutically-acceptable salt, biohydrolyzable amide or biohydrolyzable ester thereof. In other aspects, the invention is directed to pharmaceutical compns. containing the above compds. and to methods of treating diseases characterized by matrix metalloprotease activity using these compds. or the pharmaceutical compns. containing them. Eight of the hydroxamic acid containing inhibitors were synthesized.

IT *141907-41-7*, Matrix *metalloproteinase*
RL: MSC (Miscellaneous)
(hydroxamic acid-containing *inhibitors* of matrix metalloproteases and their use in pharmaceuticals)
RN 141907-41-7 HCAPLUS
CN Proteinase, matrix metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(hydroxamic acid-containing inhibitors of matrix metalloproteases and their use in pharmaceuticals)
RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 22 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1996:488746 HCAPLUS Full-text
DOCUMENT NUMBER: 125:143329
TITLE: Preparation of peptide *metalloproteinase inhibitors*
INVENTOR(S): Beckett, Raymond Paul; Whittaker, Mark; Miller, Andrew; Martin, Fionna Mitchell
PATENT ASSIGNEE(S): British Biotech Pharmaceuticals Limited, UK
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9616931	A1	19960606	WO 1995-GB2770	19951127 <--
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RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
TW 382620	B	20000221	TW 1995-84107403	19950718 <--
CA 2205972	A1	19960606	CA 1995-2205972	19951127 <--
AU 9539332	A	19960619	AU 1995-39332	19951127 <--
AU 688164	B2	19980305		
GB 2308844	A	19970709	GB 1997-6212	19951127 <--
GB 2308844	B	19980902		
EP 793641	A1	19970910	EP 1995-937128	19951127 <--
EP 793641	B1	19990421		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
BR 9509823	A	19971104	BR 1995-9823	19951127 <--
CN 1166825	A	19971203	CN 1995-196436	19951127 <--
HU 77221	A2	19980302	HU 1997-1678	19951127 <--
JP 11501288	T	19990202	JP 1995-5_8419	19951127 <--
AT 179165	T	19990515	AT 1995-937128	19951127 <--
ES 2131342	T3	19990716	ES 1995-937128	19951127 <--
US 5866717	A	19990202	US 1997-836839	19970521 <--
FI 9702198	A	19970523	FI 1997-2198	19970523 <--
NO 9702379	A	19970523	NO 1997-2379	19970523 <--
PRIORITY APPLN. INFO.:			GB 1994-23914 A	19941126 <--
			WO 1995-GB2770 W	19951127 <--

OTHER SOURCE(S): MARPAT 125:143329
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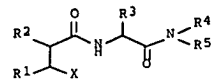


I

AB Peptides I (X = CO2H, CONHOH; R1 = H, alkyl, alkenyl, (un)substituted Ph, heterocyclyl; R2 = alkyl, alkenyl, alkynyl, Bn, cycloalkyl, cycloalkenyl, heterocyclyl, alkoxy; R3 = amino acid, alkyl, alkenyl, alkynyl, halogen, heterocyclyl; R4 = alkoxyalkyl, alkyl; R5 = H, alkyl) were prepared as water soluble matrix *metalloproteinase inhibitors*. Thus,.

IT *9001-12-1*, Collagenase *79955-99-0*, Stromelysin 1
146480-35-5, Gelatinase A
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of peptide *metalloproteinase inhibitors*)
RN 9001-12-1 HCAPLUS
CN Collagenase (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 79955-99-0 HCAPLUS
CN Stromelysin 1 (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 146480-35-5 HCAPLUS
CN Gelatinase A (CA INDEX NAME)

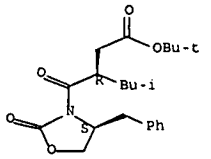
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *144287-83-2P*

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of peptide *metalloproteinase inhibitors*)

RN 144287-83-2 HCAPLUS

CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 23 OF 33 HCAPLUS. COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:978678 HCAPLUS Full-text
DOCUMENT NUMBER: 124:30412
TITLE: Preparation of carbamoylhexanohydroxamic acids as *metalloproteinase inhibitors*
INVENTOR(S): Beckett, Raymond Paul; Whittaker, Mark; Miller, Andrew
PATENT ASSIGNEE(S): British Biotech Pharmaceuticals Ltd., UK
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9519961	A1	19950727	WO 1995-GB121	19950123 <--
W: AU, BR, CA, CN, CZ, DE, FI, GB, HU, JP, KR, NO, NZ, PL, RU, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2181709	A1	19950727	CA 1995-2181709	19950123 <--
AU 9514603	A	19950808	AU 1995-14603	19950123 <--
AU 678884	B2	19970612		
GB 2300188	A	19961030	GB 1996-11282	19950123 <--
GB 2300188	B	19980701		
EP 740655	A1	19961106	EP 1995-906403	19950123 <--
EP 740655	B1	19991020		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
HU 74511	A2	19970128	HU 1996-1987	19950123 <--
JP 09508362	T	19970826	JP 1995-519424	19950123 <--
JP 3827324	B2	20060927		
GB 2315750	A	19980211	GB 1997-21061	19950123 <--
GB 2315750	B	19980701		
EP 905126	A1	19990331	EP 1998-121251	19950123 <--
EP 905126	B1	20021204		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				

AT 185798	T	19991115	AT 1995-906403	19950123 <--
ES 2139183	T3	20000201	ES 1995-906403	19950123 <--
AT 228999	T	20021215	AT 1998-121251	19950123 <--
FI 9602905	A	19960719	FI 1996-2905	19960719 <--
NO 9603031	A	19960920	NO 1996-3031	19960719 <--
US 5902791	A	19990511	US 1996-676359	19960722 <--
AU 9716540	A	19970522	AU 1997-16540	19970325 <--
AU 711047	B2	19991007		
US 6017889	A	20000125	US 1998-219704	19981223 <--
GR 3032337	T3	20000427	GR 2000-400035	20000112 <--

PRIORITY APPLN. INFO.:	GB 1994-1416	A	19940122 <--
	GB 1994-13566	A	19940706 <--
	EP 1995-906403	A3	19950123 <--
	GB 1996-11282	A3	19950123 <--
	WO 1995-GB121	W	19950123 <--
	US 1996-676359	A3	19960722 <--

OTHER SOURCE(S): CASREACT 124:30412; MARPAT 124:30412

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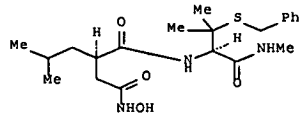


I

AB R1CH(COR)CHR2CCONHCHR3CONR4R5 [R = OH, NHOH; R1 = H, alkyl, phenylalkyl, etc.; R2 = (phenyl)alkyl, heteroarylalkyl, etc.; R3 = CR6R7R8, CR9R10R11; R4 = H, (un)substituted alkyl; R5 = H, alkyl; R6-R8 = alk(en)yl, phenylalkyl, etc.; R6R7 = atoms to form a ring; R9,R10 = alk(en)yl, phenylalkyl, OH, CO2H, etc.; R11 = H, OH, halo, CO2H, etc.] were prepared as *metalloproteinase inhibitors* (no data). Thus, 4-methylvaeroyl chloride was amidated by (S)-4-benzyloxazolidin-2-one and the product alkylated by BrCH2CO2CMe3 to give, after hydrolysis, (R)-Me3CO2CCH2CH(CH2CHMe2)CO2H which was amidated by (S)-PhCH2SCMe2CH(NH2)CONHMe to give, after saponification and H2NOH amidation, title compound I.

IT *81669-70-7, Metalloproteinase*
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(mediated diseases; treatment; preparation of carbamoylhexanohydroxamic acids as *metalloproteinase inhibitors*)

RN 81669-70-7 HCAPLUS

CN Proteinase, metallo- (CA INDEX NAME)

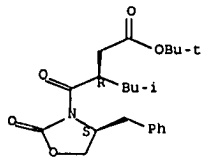
*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of carbamoylhexanohydroxamic acids as *metalloproteinase inhibitors*)

RN 144287-83-2 HCAPLUS

CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 24 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1995:401186 HCAPLUS Full-text
DOCUMENT NUMBER: 122:188173
TITLE: Preparation of amino acids containing hydroxamic acid moieties as *metalloproteinase inhibitors*
INVENTOR(S): Crimmin, Michael John; Beckett, Paul Raymond; Davis, Mark Hampton
PATENT ASSIGNEE(S): British Bio-Technology Ltd., UK
SOURCE: PCT Int. Appl., 43 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE	
WO 9421625	A1	19940929	WO 1994-GB495	19940314	<--
W: AU, BR, CA, CN, CZ, DE, FI, GB, HU, JP, KR, NO, NZ, RU, UA, US					
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE					
CA 2158352	A1	19940929	CA 1994-2158352	19940314	<--
AU 9462131	A	19941011	AU 1994-62131	19940314	<--
AU 671724	B2	19960905			
EP 689538	A1	19960103	EP 1994-909201	19940314	<--
EP 689538	B1	19980812			
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE					
GB 2290543	A	19960103	GB 1995-17704	19940314	<--
GB 2290543	B	19960522			
JP 08508027	T	19960827	JP 1994-520761	19940314	<--
AT 169621	T	19980815	AT 1994-909201	19940314	<--
FI 9504351	A	19950915	FI 1995-4351	19950915	<--
NO 9503652	A	19950915	NO 1995-3652	19950915	<--
US 5652262	A	19970729	US 1995-513868	19951201	<--

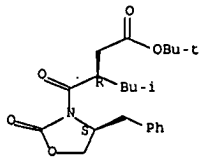
PRIORITY APPLN. INFO.:		GB 1993-5348	A	19930316 <--
		GB 1993-20360	A	19931002 <--
		WO 1994-GB495	W	19940314 <--

OTHER SOURCE(S): MARPAT 122:188173
AB Title compds. H2CCHCH2CH(HONHCO)CHR2CONHCHR3CONR4R5 (R2 = C2-6 alkyl which may contain an ether or thioether linkage; R3 = the side chain of a naturally occurring α-amino acid in which any carboxylic acid group may be esterified or amidated, HO, HS which may be acylated or alkylted (etherified), amino which may be acylated, etc.; R4 = H, Me; R5 = H, C1-6 alkyl, Ph-C1-C6 alkyl) or a

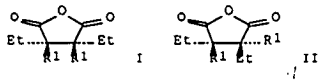
salt, solvate or hydrate thereof, useful in treatment or prophylaxis of disease or conditions mediated by matrix *metalloproteinases* and tumor necrosis factor from cells, are prepared 4S-(phenylmeth)oxazolidin-2-one was reacted with 4-methylvaleric acid chloride to give N-(4-methylpenyanoyl)-4S-(phenylmethyl)oxazodinin-2- one which in 5 steps was converted to (RS:RR)-allyl-2R-isobutyl-1,4-dioic 1-pentafluorophenyl 4-tert-Bu diester which was reacted with S-phenylalanine methylamide in DMF to give a product to which was added TFA to give the title compound 3R-(2-phenyl-1S-methylcarbamoyl-ethylcarbamoyl)-5-methyl-2S-propenylhexanohydroxamic acid.
IT *81669-70-7*
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(preparation of amino acids containing hydroxamic acid moieties as *metalloproteinase inhibitors*)
RN 81669-70-7 HCAPLUS
CN Proteinase, metallo- (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
IT *144287-83-2P*
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of amino acids containing hydroxamic acid moieties as *metalloproteinase inhibitors*)
RN 144287-83-2 HCAPLUS
CN 3-Oxazolidinebutanoic acid, β-(2-methylpropyl)-γ,2-dioxo-4-(phenylmethyl)-, 1,1-dimethylethyl ester, (βR,4S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L91 ANSWER 25 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1988:630666 HCAPLUS Full-text
DOCUMENT NUMBER: 109:230666
TITLE: Sterically-driven anhydride formation
AUTHOR(S): Belletire, J. L.; Conroy, G. M.
CORPORATE SOURCE: Dep. Chem., Univ. Cincinnati, Cincinnati, OH, 45221-0172, USA
SOURCE: Synthetic Communications (1988), 18(4), 403-15
CODEN: SYNCAV; ISSN: 0039-7911
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 109:230666
GI

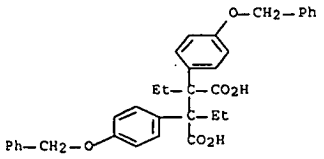


AB Acids R1CHEtCO2H (R1 = 4-PhCH2OC6H4, p-anisyl) were treated with BuLi, (Me2CH)2NH, and iodine to give anhydrides I and II. The methoxy acid was also converted to diethylstilbestrol.

IT *117726-66-6P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 117726-66-6 HCAPLUS

CN Butanedioic acid, 2,3-diethyl-2,3-bis[4-(phenylmethoxy)phenyl]- (9CI) (CA INDEX NAME)



L91 ANSWER 26 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1978:443095 HCAPLUS Full-text

DOCUMENT NUMBER: 89:43095

TITLE: Phenoxyhydroxypropylamines

INVENTOR(S): Teulon, Jean Marie

PATENT ASSIGNEE(S): Hexachimie S. A., Fr.

SOURCE: Ger. Offen., 76 pp.
CODEN: GWXXBX

DOCUMENT TYPE: Patent

LANGUAGE: German

FAMILY ACC. NUM. COUNT: 1

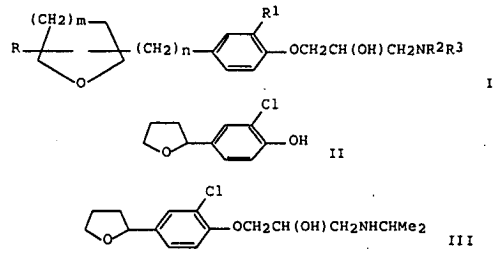
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
DE 2733305	A1	19780126	DE 1977-2733305	19770721
FR 2359135	A1	19780217	FR 1977-20380	19770701
NL 7707949	A	19780124	NL 1977-7949	19770715
ZA 7704301	A	19780628	ZA 1977-4301	19770718
ES 460866	A1	19780816	ES 1977-460866	19770719
AU 7727141	A	19790125	AU 1977-27141	19770719
BE 856966	A1	19780120	BE 1977-56099	19770720
DK 7703295	A	19780123	DK 1977-3295	19770720
SE 7708368	A	19780123	SE 1977-8368	19770720
NO 7702604	A	19780124	NO 1977-2604	19770721
JP 53012851	A	19780204	JP 1977-88268	19770722

PRIORITY APPLN. INFO.: GB 1976-30647 A 19760722
GB 1976-53576 A 19761222

OTHER SOURCE(S): MARPAT 89:43095

GI

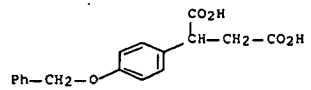


AB Phenoxypropanolamines I (R = H, alkyl, cycloalkyl; R1 = H, halogen, alkyl, cycloalkyl, allyl, NO2, Ac; R2, R3 = H, alkyl, dimethoxyphenethyl, CMe2Ph; m = 1,2; n = 0-3) were prepared Thus 3,4-Cl(MeO)C6H3COCH2CH2CO2H was demethylated, 3,4-Cl(HO)C6H3COCH2CH2CO2H reduced to butyrolactone and then to THF which was treated with epichlorohydrin, followed by Me2CHNH2 to give III. I had β-sympatholytic heart stimulant activity.

IT *66123-34-0 66123-61-3*
RL: RCT (Reactant); RACT (Reactant or reagent)
(reduction of)

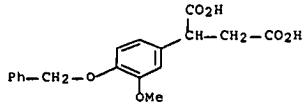
RN 66123-34-0 HCAPLUS

CN Butanedioic acid, [4-(phenylmethoxy)phenyl]- (9CI) (CA INDEX NAME)



RN 66123-61-3 HCAPLUS

CN Butanedioic acid, [3-methoxy-4-(phenylmethoxy)phenyl]- (9CI) (CA INDEX NAME)

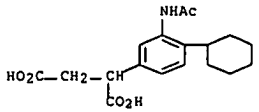


L91 ANSWER 27 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1972:547453 HCAPLUS Full-text
DOCUMENT NUMBER: 77:147453
TITLE: 5-Substituted-1-indancarboxylic acids as potential antiinflammatory agents
AUTHOR(S): Allen, George R., Jr.; Littell, Ruddy; McEvoy, Francis J.; Sloboda, Adolph E.
CORPORATE SOURCE: Lederle Lab., A Div., Am. Cyanamid Co., Pearl River, NY, USA
SOURCE: Journal of Medicinal Chemistry (1972), 15(9), 934-7
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

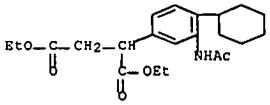
AB 5-Isopropyl-1-indancarboxylic acid [34177-55-4] and 5-cyclohexyl-1-indancarboxylic acid (I) [31962-05-7] suppressed carrageenin-induced rat paw edema and uv-induced erythema in guinea pigs at 250 mg/kg orally, but were less active than indomethacin in these assays and did not suppress adjuvant-induced arthritis or promote weight gain in rats. To synthesize I, 4-cyclohexylbenzaldehyde was reacted with Et cyanoacetate to yield an α-cyanocinnamate; Michael addition of cyanide and acid hydrolysis yielded a substituted phenylsuccinic acid; Friedel-Crafts ring closure with HF gave a 3-indanone derivative, which was converted to I by Clemmensen reduction Zn amalgam.

IT *38913-13-2P 38913-20-1P*
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

RN 38913-13-2 HCAPLUS
CN Butanedioic acid, [3-(acetylamino)-4-cyclohexylphenyl]- (9CI) (CA INDEX NAME)



RN 38913-20-1 HCAPLUS
CN Butanedioic acid, [3-(acetylamino)-4-cyclohexylphenyl]-, diethyl ester (9CI) (CA INDEX NAME)



L91 ANSWER 28 OF 33 HCAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1959:45266 HCAPLUS
DOCUMENT NUMBER: 53:45266
ORIGINAL REFERENCE NO.: 53:8163i,8164a-e
TITLE: Substituted pyrrolidines
INVENTOR(S): Villani, Frank J.; Sperber, Nathan
PATENT ASSIGNEE(S): Schering Corp.
DOCUMENT TYPE: Patent
LANGUAGE: Unavailable
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2852526		19580916	US 1955-505834	19550503

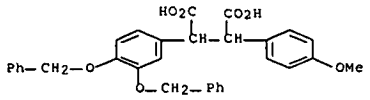
AB Diphenylpyrrolidines were prepared by reduction of diphenylsuccinimides with LiAlH4 or by catalytic hydrogenation. Thus, 30 g. N-methyl-3,4-diphenylsuccinimide in 300 ml. anhydrous Et2O was added to a stirred suspension of 18 g. LiAlH4 in 1.2 l. refluxing anhydrous Et2O, the mixture stirred and refluxed 16 hrs., cooled, and decomposed with H2O in the usual manner and thoroughly extracted with Et2O, the Et2O exts. were dried and the solvent distilled in vacuo to give 22 g. 1-methyl-3,4-diphenylpyrrolidine, b2 162-4°; HCl salt m. 194-6°; MeBr salt m. 190-1°. Also prepared were the following substituted-3,4-diphenylpyrrolidines: 1-Pr, b2 160-4°, HCl salt, m. 202-3°, MeI salt, m. 209-10°; 1-iso-Pr, b5 187-90°, HCl salt, m. 158-9°, MeBr salt, m. 255-56°, MeI salt, m. 215-6°; 1-allyl, b1 167-71°, MeI salt, m. 186-7°, HCl salt, m. 160-1°; 1-(2-hexyl), b1 174-6°; PhCH2, b2 208-9°, HCl salt, m. 230-1°, MeBr salt, m. 199-200°; 1-[2-(p-methoxyphenyl)propyl], MeBr salt; 1-iso-Pr-2-Me, b1 169-72°; 1-iso-Pr 2-Me 4-OH, acid succinate, MeI salt. The following pyrrolidines were prepared (substituents listed): 1-iso-Pr, 3-(p-ClC6H4), 4-Ph, b1 175-8°, MeI salt, m. 201-2°; 1-Pr, 3-Ph 4-[3,4(MeO)2C6H3], b1 190-3°, MeI salt, m. 98-102°; 1-iso-Pr,3-(o-MeOC6H4), 4-Ph, b1.5 170-1°, HCl salt, MeBr salt; 1-iso-Pr, 3-[3,4-(MeO)2C6H3], 4-Ph, b3 185-90°, Me2SO4 salt, HCl salt; 1-iso-Pr, 3-[3,4-(HO2)C6H3], 4-,p-MeOC6H4), EtBr salt; 1-iso-Pr, 3-(o-BrC6H4), 4-Ph, b1 185-89°, acid tartrate, iso-PrI salt; 1-iso-Pr, 3-[3,4-(HO)2C6H3], 4-[3,4-(MeO)2C6H3], HBr salt; 1-iso-Pr, 3(p-ClC6H4), 4-[3,4-(MeO)2C6H3], maleate, MeI salt, Et2SO4 salt; 1-Pr 3(o-MeOC6H4), 4-(o-MeOC6H4), EtBr salt; 1-(2-hexyl), 3-(m-MeC6H4) 4-Ph, b2 168-70°, salicylate, MeBr salt; 2-Me, 3,4-Ph2, b6 172-76°, HCl salt, m. 197-8°; 1-iso-Pr, 2-Me, 3,4-Ph2, b2 180-5°; 1-iso-Pr, 3,4-Ph2, 2-Me, 4-HO, b1 176-80°, acid succinate, MeI salt. The following succinonitriles, acids, and imides with their respective m.ps. were prepared: α,β-(o-MeOC6H4)2, -, -, -; N-(2-hexyl) 3,4-Ph2, -, -, 90-2°; α-Ph, β-(p-ClC6C4), 229-30°, 249-50°, -; α-Ph, β-[3,4-(MeO)2C6H3], 199-200°, 239-40°, 87-8°; N-benzyl, 3,4-Ph2, -, -, 85-7°; α-(p-MeOC6H4CHMeCH2), β-3,4-Ph2, -, -, 146-7°; α-(o-MeOC6H4), β-Ph, -, -, -; α-Ph, β[3,4-(MeO)2C6H3], -, -, -; α-[3,4-(PhCH2O)2C6H3], β-(p-MeOC6H4), -, -, -; α-Ph, β-(o-BrC6H4), -, -, -; α-(p-ClC6H)4), β-[3,4-(MeO)2C6H3], -, -, -; α-Ph,

β-(m-MeC6H4), -, -, -. Di-Et β-phenyl-β-(2-isopentyl) succinate was prepared These compds. are valuable as antihistamines, anticholinergic and bronchodilator compds.

IT *103271-91-6P*, Succinic acid, 2-[3,4-bis(benzyloxy)phenyl]-3-(p-methoxyphenyl)-
RL: PREP (Preparation)
(preparation of)

RN 103271-91-6 HCAPLUS

CN Succinic acid, 2-[3,4-bis(benzyloxy)phenyl]-3-(p-methoxyphenyl)- (6CI) (CA INDEX NAME)



L91 ANSWER 29 OF 33 MARPAT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 143:306496 MARPAT Full-text
TITLE: Preparation of glucopyranose compounds containing fused heterocycle moiety as SGLT inhibitors
INVENTOR(S): Fushimi, Nobuhiko; Fujikura, Hideki; Isaji, Masayuki
PATENT ASSIGNEE(S): Kissei Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

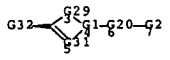
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005085265	A1	20050915	WO 2005-JP4152	20050303
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005219777	A1	20050915	AU 2005-219777	20050303
CA 2557320	A1	20050915	CA 2005-2557320	20050303
EP 1724277	A1	20061122	EP 2005-720423	20050303
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				
CN 1934122	A	20070321	CN 2005-80006211	20050303
PRIORITY APPLN. INFO.:			JP 2004-61429	20040304

GI

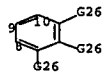
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. I [one of R1 and R4 represents II; the other represents H, OH, halo, etc.; R5, R6 = H, OH, halo, etc.; Q = alkylene, alkenylene, alkynylene, etc.; ring A = aryl, heteroaryl; R2, R3 = H, OH, halo, etc.;, A1 = O, S, NR9; R9 = H, alkyl; A2 = N, CH; G = III, etc.; E1 = H, F, OH; E2 = H, F, Me, etc.] were prepared For example, treatment of 2,3,4,6-tetra-O-benzyl-1-[4-(2-phenylethyl)benzo[b]thiophen-2-yl]-D- glucopyranose, e.g., prepared from 1-bromo-3-fluorobenzene in 6 steps, with triethylsilane in the presence of BF3·OEt2 followed by debenzylation using ethanethiol and BF3·OEt2 gave 2-(β-D-glucopyranosyl)-4-(2-phenylethyl)benzo[b]thiophene (IV). In SGLT1 (sodium dependent glucose transporter-1) inhibition assays, compound IV exhibited the IC50 value of 220 nM. Compds. I are claimed useful for the treatment of diabetes, obesity, etc.

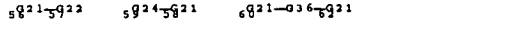
MSTR 1



G1 = 9-3 8-5 10-6



G2 = Ph
G20 = 56-4 57-7 / 59-4 58-7 / 60-4 62-7



G21 = CH2
G24 = O
G26 = alkyl <containing 1-6 C>
(opt. substd. by 1 or more G27) /
alkoxy <containing 1-6 C> (opt. substd. by 1 or more G28)
G27 = CO2H
Patent location: claim 1
Note: or pharmacologically acceptable salts or prodrugs
Note: additional heteroatom interruption or oxo or ring

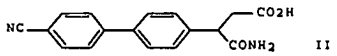
formation also claimed

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 30 OF 33 MARPAT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 142:261292 MARPAT Full-text
TITLE: Preparation of (hetero)aryl-substituted succinate derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Holmes, Ian; Watson, Stephen Paul
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 36 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005016868	A2	20050224	WO 2004-EP9087	20040812
WO 2005016868	A3	20050519		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1654218	A2	20060510	EP 2004-764084	20040812
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
JP 2007502259	T	20070208	JP 2006-522996	20040812
US 2006235074	A1	20061019	US 2006-569812	20060210
PRIORITY APPLN. INFO.:			GB 2003-19069	20030814
			WO 2004-EP9087	20040812

OTHER SOURCE(S): CASREACT 142:261292
GI

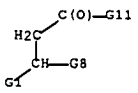


II

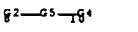
AB Title compds. represented by the formula I, R1ZQCH(R2)CH2X, [wherein R1 = (un)substituted alkyl(cycloalkyl), alkylheterocycloalkyl, alkylaryl, etc.; Z = a bond, CH2, O, S, etc.; Q = (un)substituted (hetero)aryl; X = COR3; R2 = CONH2, CO2H, sulfonylamino, etc.; R3 = OH, oxyalkyl or (un)substituted amino; with a proviso; and physiol. functional derivs. thereof] were prepared as matrix metalloproteinase (MMP) inhibitors. Coupling reaction of 4-amino-3-(4-bromophenyl)-4-oxobutanoic acid with p-nitrilephenylboronic acid gave II in

100% yield. I showed inhibition of MMP-12 with IC50 values of below 100 μM. Thus, I and their pharmaceutical compns. are useful as matrix metalloproteinase inhibitors for the treatment of inflammation or autoimmune disease (no data).

MSTR 1



G1 = 10



G2 = Ph (opt. substd. by (up to 1) G13)
G4 = phenylene
G5 = 18-8 17-10

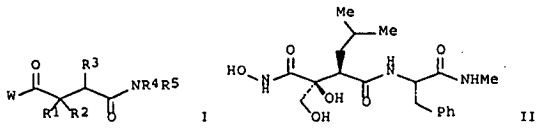
G8 = CO2H
G11 = OH
G14 = CH2
Patent location: claim 1
Note: substitution is restricted
Note: also incorporates claim 10, structures II, III and VI

L91 ANSWER 31 OF 33 MARPAT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 129:175968 MARPAT Full-text
TITLE: Preparation of water-soluble hydroxysuccinate derivatives as matrix metalloproteinase inhibitors
INVENTOR(S): Alpegiani, Marco; Palladino, Massimiliano; Corigli, Riccardo; Jabes, Daniela; Perrone, Ettore; Abrate, Francesca; Bissolino, Pierluigi; Lombroso, Marina
PATENT ASSIGNEE(S): Pharmacia & Upjohn S.p.A., Italy
SOURCE: PCT Int. Appl., 132 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9833788	A1	19980806	WO 1998-EP531	19980123
W: AU, BR, CA, CN, HU, IL, JP, KR, MX, NO, NZ, PL, UA, US, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CN 1223636	A	19990721	CN 1997-195888	19970620
AU 9862942	A	19980825	AU 1998-62942	19980123
EP 960108	A1	19991201	EP 1998-906901	19980123
EP 960108	B1	20041027		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, NL, SE, PT, IE, FI				
JP 2001511139	T	20010807	JP 1998-532543	19980123
AT 280763	T	20041115	AT 1998-906901	19980123
ES 2231965	T3	20050516	ES 1998-906901	19980123
US 6194451	B1	20010227	US 1999-355315	19990730
PRIORITY APPLN. INFO.:			GB 1997-2088	19970131
			WO 1998-EP531	19980123

GI

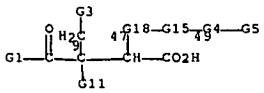


I

II

AB A title compds. I [W = NHOH or OH, R1 = (un)protected CH2OH, CH2SH, or derivs. thereof; R2 = (un)protected OH; R3, R4 = organic group; R5 = H, Me; NR4R5 = azaheterocyclyl], and the solvates, hydrates and pharmaceutically acceptable salts thereof, can inhibit matrix metalloproteinases (MMP) and the release of tumor necrosis factor (TNF). Processes for producing the compound, intermediates involved in the processes, and pharmaceutical compns. containing the compound are also described. Thus II, prepared in several steps from DL-leucine, dibenzyl malonate, and L-phenylalanine methylamide, inhibited MMP-1, MMP-2, and MMP-3 with Ki = 1.5 nM, 3.1 nM, and 32 nM, resp.

MSTR 2A



G1 = OH
G4 = alkylene <containing 1-5 C, unbranched>
G5 = biphenylyl (opt. substd.)
G15 = O
G18 = phenylene

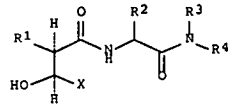
Patent location: claim 11

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L91 ANSWER 32 OF 33 MARPAT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 127:81790 MARPAT Full-text
TITLE: Synthesis of carboxamide-derivative matrix metalloproteinase inhibitors
INVENTOR(S): Reeve, Maxwell; Bowles, Stephen Arthur
PATENT ASSIGNEE(S): British Biotech Pharmaceuticals Limited, UK; Reeve, Maxwell; Bowles, Stephen Arthur
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9719050	A1	19970529	WO 1996-GB2820	19961118
W: AU, BR, CA, CN, CZ, GB, HU, IL, JP, KR, MX, NO, NZ, PL, TR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9675823	A	19970611	AU 1996-75823	19961118
GB 2321459	A	19980729	GB 1998-6358	19961118
EP 861226	A1	19980902	EP 1996-938374	19961118
EP 861226	B1	20000223		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2000500759	T	20000125	JP 1997-519481	19961118
AT 189886	T	20000315	AT 1996-938374	19961118
ES 2144271	T3	20000601	ES 1996-938374	19961118
US 5986132	A	19991116	US 1998-68676	19980514
PRIORITY APPLN. INFO.:			GB 1995-23637	19951118
			WO 1996-GB2820	19961118

GI



I

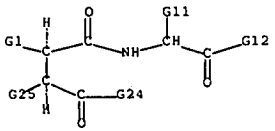
AB The title compds. [I; R1 = (un)substituted alkyl, (un)substituted alkenyl, (un)substituted alkynyl, phenylalkoxy, etc.; R2 = (un)natural α-amino acid; R3 = H, alkyl; R4 = H, alkyl, perfluoroalkyl, (un)substituted NH2, (un)substituted Ph or heteroaryl; X = carboxylic acid groups or salts], useful as matrix metalloproteinase inhibitors (no data), are prepared Thus, 3R-(2,2-dimethyl-1S-methylcarbamoylpropylcarbamoyl)-2S- hydroxy-5-methylhexanohydroxamic acid was prepared from 2-benzyloxycarbonyl- 3R-isobutylsuccinic acid 1-benzyl ester in 6 steps.

MOST RECENT CITATIONS FOR PATENTS FROM MAJOR ISSUING AGENCIES
(COVERAGE TO THESE DATES IS NOT COMPLETE):

US	2007032719	08 FEB	2007
DE	102006011317	15 FEB	2007
EP	1750119	07 FEB	2007
JP	2007035357	08 FEB	2007
WO	2007022718	01 MAR	2007
GB	2428675	07 FEB	2007
FR	2889524	09 FEB	2007
RU	2293086	10 FEB	2007
CA	2552059	19 JAN	2007

Expanded G-group definition display now available.

MSTR 1



G12 = 25

G15 = Ph (opt. substd. by 1 or more G19)
G19 = alkyl <containing 1-6 C>
(substd. by alkoxycarbonyl <containing 1-6 C>) /
alkylcarbonylamino <containing 1-6 C> /
alkyl (opt. substd. by 1 or more G21) /
Ph (opt. substd. by 1 or more G22)
G21 = CO2H
Derivative: or salts
Patent location: claim 1

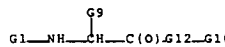
L91 ANSWER 33 OF 33 MARPAT COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 126:212449 MARPAT Full-text
TITLE: Metalloproteinase inhibitors
INVENTOR(S): Floyd, Christopher David; Beckett, Raymond Paul; Whittaker, Mark; Miller, Andrew
PATENT ASSIGNEE(S): British Biotech Pharmaceuticals Limited, UK; Floyd, Christopher David; Beckett, Raymond Paul; Whittaker, Mark; Miller, Andrew
SOURCE: PCT Int. Appl., 58 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9703783	A1	19970206	WO 1996-GB1737	19960722
W: AU, BR, CA, CN, CZ, GB, GE, HU, IL, JP, KR, MX, NZ, PL, RU, SG, SK, TR, UA, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
AU 9666633	A	19970218	AU 1996-66633	19960722
GB 2318353	A	19980422	GB 1998-151	19960722
GB 2318353	B	19991006		
EP 865339	A1	19980923	EP 1996-926462	19960722
EP 865339	B1	20030122		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

JP 11510140	T	19990907	JP 1996-506444	19960722
AT 231520	T	20030215	AT 1996-926462	19960722
US 6103739	A	20000815	US 1998-37	19980422
PRIORITY APPLN. INFO.:			GB 1995-14867	19950720
			WO 1996-GB1737	19960722

AB Peptides R1CHR2CONHCHR3CONR4R5 [R1 = R6SCHR7CONH or OCHN(OH)CHR7 (R6 = H, acyl; R7 = H, R2); R2 = (Alk)m-Qn-Z (m, n = 0, 1; Alk = alkyl, alkenyl, alkynyl; Q = O, S, SO, SO2; Z = H, acyl, optionally substituted alkyl, cycloalkyl, alkenyl, cycloalkenyl, Ph, or heterocyclyl); R3 = amino acid side chain in which any functional group may be protected; R4 = Ph, heterocyclyl; R5 = H, alkyl] were prepared for use as matrix metalloproteinase inhibitors. Thus, 2RS-mercaptohexanoic acid {3-methyl-1S-[2-phenyl-1S-(thiazol-2-ylcarbamoyl)ethylcarbamoyl]butyl}amid e was prepared by sequential coupling-deprotection of Boc-S-phenylalanine (Boc = tert-butoxycarbonyl), 2-aminothiazole, Boc-S-leucine, and 2RS-thioacetylhexanoic acid.

MSTR 1



G10 = Ph (opt. substd. by 1 or more G16)
G16 = alkyl <containing 1-6 C>
(substd. by alkoxycarbonyl <containing 1-6 C>) /
alkylcarbonylamino <containing 1-6 C> / Ph (opt. substd.)
Derivative: or salts, hydrates or solvates
Patent location: claim 1

=> d his full

(FILE 'HOME' ENTERED AT 09:28:31 ON 26 MAR 2007)

FILE 'HCAPLUS' ENTERED AT 09:29:35 ON 26 MAR 2007

FILE 'HCAPLUS' ENTERED AT 09:30:02 ON 26 MAR 2007
E US2006-569812/APPS
L1 1 SEA ABB=ON PLU=ON US2006-569812/AP
D SCAN
SEL RN L1

FILE 'REGISTRY' ENTERED AT 09:32:21 ON 26 MAR 2007
L2 45 SEA ABB=ON PLU=ON (107-82-4/BI OR 126747-14-6/BI OR 127152-98-1/BI OR 14199-15-6/BI OR 156-38-7/BI OR 1647-26-3/BI OR 18162-48-6/BI OR 1878-68-8/BI OR 27727-37-3/BI OR 33155-58-7/BI OR 335200-36-7/BI OR 5292-43-3/BI OR 5437-45-6/BI OR 55784-09-3/BI OR 845785-97-9/BI OR 845785-98-0/BI OR 845785-99-1/BI OR 845786-00-7/BI OR 845786-01-8/BI OR 845786-02-9/BI OR 845786-03-0/BI OR 845786-04-1/BI OR 845786-06-3/BI OR 845786-07-4/BI OR 845786-08-5/BI OR 845786-09-6/BI OR 845786-10-9/BI OR 845786-11-0/BI OR 845786-12-1/BI OR 845786-13-2/BI OR 845786-14-3/BI OR 845786-15-4/BI OR 845786-16-5/BI OR 845786-17-6/BI OR 845786-18-7/BI OR 845786-19-8/BI OR 845786-20-1/BI OR 845786-21-2/BI OR 845786-22-3/BI OR 845786-23-4/BI OR 845786-24-5/BI OR 845786-25

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L51           0 SEA ABB=ON  PLU=ON  L47 NOT L28
L52           0 SEA ABB=ON  PLU=ON  L49 NOT L30

     FILE 'REGISTRY' ENTERED AT 10:24:52 ON 26 MAR 2007
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               D BROW L30
L53           1 SEA ABB=ON  PLU=ON  66123-34-0
L54           0 SEA ABB=ON  PLU=ON  66123-34-0/CRN

     FILE 'HCAPLUS' ENTERED AT 10:26:44 ON 26 MAR 2007
L55           1 SEA ABB=ON  PLU=ON  L53
L56           4 SEA ABB=ON  PLU=ON  (L43 OR L55)

     FILE 'REGISTRY' ENTERED AT 10:26:58 ON 26 MAR 2007
L57           4 SEA ABB=ON  PLU=ON  (L27 OR L28 OR L33 OR L53)
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L58        1373 SEA ABB=ON  PLU=ON  C18 H18 O6/MF
L59        1659 SEA ABB=ON  PLU=ON  C17 H16 O5/MF
L60         549 SEA ABB=ON  PLU=ON  C22 H31 N O5/MF
L61        1469 SEA ABB=ON  PLU=ON  C18 H23 N O5/MF
L62        5050 SEA ABB=ON  PLU=ON  (L58 OR L59 OR L60 OR L61)

     FILE 'HCAPLUS' ENTERED AT 10:28:38 ON 26 MAR 2007
L63        6773 SEA ABB=ON  PLU=ON  L62
               E METALLOPROTEINASE/CT
               E E3+ALL
L64       33837 SEA ABB=ON  PLU=ON  METALLOPROTEINASE+NT/CT
               E METALLOPROTEINASE/CT
L65       25598 SEA ABB=ON  PLU=ON  METALLOPROTEINASE?
L66          47 SEA ABB=ON  PLU=ON  L63 AND (L64 OR L65)
L67          28 SEA ABB=ON  PLU=ON  L66 AND (METALLOPROTEINASE?(L)INHIBIT?)
               D KWIC
               D KWIC 2
L68          24 SEA ABB=ON  PLU=ON  L67 AND (PY<2005 OR AY<2005 OR PRY<2005)

     FILE 'MARPAT' ENTERED AT 10:30:35 ON 26 MAR 2007
L69           5 SEA SSS SAM L19
L70         201 SEA SSS FUL L19
L71           4 SEA SSS SAM L20
L72         163 SEA SSS FUL L20
L73           6 SEA SSS SAM L21
L74         268 SEA SSS FUL L21
L75           6 SEA SSS SAM L22
L76           6 SEA SSS SAM L22
L77         310 SEA SSS FUL L22
L78         199 SEA ABB=ON  PLU=ON  L70/COM
L79         161 SEA ABB=ON  PLU=ON  L72/COM
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L84         263 SEA ABB=ON  PLU=ON  L80
L85         305 SEA ABB=ON  PLU=ON  L81
L86         485 SEA ABB=ON  PLU=ON  (L82 OR L83 OR L84 OR L85,
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L88           6 SEA ABB=ON  PLU=ON  L87 AND (PY<2005 OR AY<2005 OR PRY<2005)
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     FILE 'HCAPLUS' ENTERED AT 10:35:36 ON 26 MAR 2007
L*** DEL       6 S L88

     FILE 'MARPAT' ENTERED AT 10:35:52 ON 26 MAR 2007
L89           6 SEA ABB=ON  PLU=ON  L88
L90           6 SEA ABB=ON  PLU=ON  L89 AND (L78 OR L79 OR L80 OR L81)

     FILE 'STNGUIDE' ENTERED AT 10:36:44 ON 26 MAR 2007
               D QUE L43
               D QUE L68
               D QUE L90

     FILE 'HCAPLUS, MARPAT' ENTERED AT 10:37:05 ON 26 MAR 2007
L91           33 DUP REM L43 L68 L90 (1 DUPLICATE REMOVED)
                    ANSWERS '1-28' FROM FILE HCAPLUS
                    ANSWERS '29-33' FROM FILE MARPAT
               D IBIB ABS HITSTR RETABLE L91 1-28
               D IBIB ABS QHIT L91 29-33


     FILE HOME

     FILE HCAPLUS

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     FILE COVERS 1907 - 26 Mar 2007  VOL 146 ISS 14
     FILE LAST UPDATED: 25 Mar 2007  (20070325/ED)

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

      This file contains CAS Registry Numbers for easy and accurate
      substance identification.

     FILE REGISTRY
     Property values tagged with IC are from the ZIC/VINITI data file
     provided by InfoChem.

     STRUCTURE FILE UPDATES:   25 MAR 2007  HIGHEST RN 928121-90-8
     DICTIONARY FILE UPDATES:  25 MAR 2007  HIGHEST RN 928121-90-8

     New CAS Information Use Policies, enter HELP USAGETERMS for details.

     TSCA INFORMATION NOW CURRENT THROUGH December 2, 2006

       Please note that search-term pricing does apply when
       conducting SmartSELECT searches.

     REGISTRY includes numerically searchable data for experimental and
     predicted properties as well as tags indicating availability of
     experimental property data in the original document.  For information
     on property searching in REGISTRY, refer to.
```

http://www.cas.org/ONLINE/UG/regprops.html

FILE STNGUIDE
FILE CONTAINS CURRENT INFORMATION.
LAST RELOADED: Mar 23, 2007 (20070323/UP).

FILE MEDLINE
FILE LAST UPDATED: 24 Mar 2007 (20070324/UP). FILE COVERS 1950 TO DATE.

SDI results from March 16, 17, and 20, may have been incomplete. SDIs delivered on March 24 will include any missing records. If you have questions, please contact your STN Service Center.

All regular MEDLINE updates from November 15 to December 16 have been added to MEDLINE, along with 2007 Medical Subject Headings (MeSH(R)) and 2007 tree numbers.

The annual reload will be available in early 2007.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE EMBASE
FILE COVERS 1974 TO 23 Mar 2007 (20070323/ED)

EMBASE is now updated daily. SDI frequency remains weekly (default) and biweekly.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE BIOSIS
FILE COVERS 1969 TO DATE.
CAS REGISTRY NUMBERS AND CHEMICAL NAMES (CNs) PRESENT
FROM JANUARY 1969 TO DATE.

RECORDS LAST ADDED: 21 March 2007 (20070321/ED)

FILE DRUGU
FILE LAST UPDATED: 23 MAR 2007 <20070323/UP>
>>> DERWENT DRUG FILE (SUBSCRIBER) <<<

>>> FILE COVERS 1983 TO DATE <<<
>>> THESAURUS AVAILABLE IN /CT <<<

FILE WPIX
FILE LAST UPDATED: 22 MAR 2007 <20070322/UP>
MOST RECENT THOMSON SCIENTIFIC UPDATE: 200720 <200720/DW>
DERWENT WORLD PATENTS INDEX SUBSCRIBER FILE, COVERS 1963 TO DATE

>>> New reloaded DWPI Learn File (LWPI) available as well <<<

>>> YOU ARE IN THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX <<<

>>> New display format FRAGHITSTR available <<<
SEE ONLINE NEWS and
http://www.stn-international.de/archive/stn_online_news/fraghitstr_ex.pdf

>>> IPC Reform backfile reclassification has been loaded to 31 December 2006. No update date (UP) has been created for the reclassified documents, but they can be identified by 20060101/UPIC and 20061231/UPIC. <<<

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http://www.stn-international.de/training_center/patents/stn_guide.pdf

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http://scientific.thomson.com/support/patents/coverage/latestupdates/

PLEASE BE AWARE OF THE NEW IPC REFORM IN 2006, SEE
http://www.stn-international.de/stndatabases/details/ipc_reform.html and
http://scientific.thomson.com/media/scpdf/ipcrdwpi.pdf

>>> FOR DETAILS ON THE NEW AND ENHANCED DERWENT WORLD PATENTS INDEX PLEASE SEE
http://www.stn-international.de/stndatabases/details/dwpi_r.html <<<

FILE BEILSTEIN
FILE LAST UPDATED ON JANUARY 10, 2007

FILE COVERS 1771 TO 2006.
FILE CONTAINS 9,780,003 SUBSTANCES

>>>PLEASE NOTE: Reaction Data and substance data are stored in separate documents and can not be searched together in one query. Reaction data for BEILSTEIN compounds may be displayed immediately with the display codes PRE (preparations) and REA (reactions). A substance answer set retrieved after the search for a chemical name, a compounds with available reaction information by combining with PRE/FA, REA/FA or more generally with RX/FA. The BEILSTEIN Registry Number (BRN) is the link between a BEILSTEIN compound and belonging reactions. For mo detailed reaction searches BRNs can be searched as reaction partner BRNs Reactant BRN (RX.RBRN) or Product BRN (RX.PBRN).<<<

>>> FOR SEARCHING PREPARATIONS SEE HELP PRE <<<

****
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* ARE BASED ON THE HIGHEST PRICE CATEGORY. THEREFORE; THESE *
* ESTIMATES MAY NOT REFLECT THE ACTUAL COSTS. *
* FOR PRICE INFORMATION SEE HELP COST *
****

NEW
* *PATENT NUMBERS (PN) AND BABS ACCESSION NUMBERS (BABSAN) CAN NOW BE SEARCHED, SELECTED AND TRANSFERRED.*
* *NEW DISPLAY FORMATS ALLREF, ALLP AND BABSAN SHOW ALL REFERENCES, ALL PATENT REFERENCES, OR ALL BABS ACCESSION NUMBERS FOR A COMPOUND AT A GLANCE.*

FILE MARPAT
FILE CONTENT: 1961-PRESENT VOL 146 ISS 12 (20070325/ED)

SOME MARPAT RECORDS ARE DERIVED FROM INPI DATA FOR 1961-1987

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                -6/BI OR 845786-26-7/BI OR 845786-27-8/BI OR 98946-18-0/BI)
                D SCAN

     FILE 'STNGUIDE' ENTERED AT 09:38:27 ON 26 MAR 2007

     FILE 'REGISTRY' ENTERED AT 09:40:53 ON 26 MAR 2007
                E 3-ACETYLAMINO-4-CYCLOHEXYLPHENYL-BUTANEDIOIC ACID/CN
                E BUTANEDIOIC ACID/CN

     FILE 'HCAPLUS' ENTERED AT 09:43:07 ON 26 MAR 2007
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L3           104 SEA ABB=ON  PLU=ON  ("HOLMES I"/AU OR "HOLMES I B"/AU OR
                "HOLMES I F"/AU OR "HOLMES I H"/AU OR "HOLMES I P"/AU OR
                "HOLMES IAN"/AU OR "HOLMES IAN B"/AU OR "HOLMES IAN D"/AU OR
                "HOLMES IAN F"/AU OR "HOLMES IAN H"/AU OR "HOLMES IAN HAMILTON"
                /AU OR "HOLMES IAN P"/AU OR "HOLMES IAN PETER"/AU)
                E WATCON S/AU
                E WATSON S/AU
L4            99 SEA ABB=ON  PLU=ON  ("WATSON S"/AU OR "WATSON S P"/AU)
                E WATSON S/AU
L5           164 SEA ABB=ON  PLU=ON  ("WATSON STEFAN"/AU OR "WATSON STEPHEN"/AU
                OR "WATSON STEPHEN PAUL"/AU OR "WATSON STEPHEN PAUL"/AU OR
                "WATSON STEVE"/AU OR "WATSON STEVE P"/AU OR "WATSON STEVEN"/AU
                OR "WATSON STEVEN P"/AU)
L6           263 SEA ABB=ON  PLU=ON  (L4 OR L5)
L7             4 SEA ABB=ON  PLU=ON  L3 AND L6
L8             6 SEA ABB=ON  PLU=ON  (L3 OR L4 OR L5) AND METALLOPROTEINASE?
L9             6 SEA ABB=ON  PLU=ON  (L7 OR L8)

     FILE 'HCAPLUS, MEDLINE, EMBASE, BIOSIS, DRUGU, WPIX' ENTERED AT 09:45:52
     ON 26 MAR 2007
L10         5752 SEA ABB=ON  PLU=ON  WATSON S?/AU
L11          587 SEA ABB=ON  PLU=ON  HOLMES I?/AU
L12            8 SEA ABB=ON  PLU=ON  L10 AND L11
L13          131 SEA ABB=ON  PLU=ON  (L10 OR L11) AND METALLOPROTEINASE?
L14           97 SEA ABB=ON  PLU=ON  L13 AND (METALLOPROTEINASE?(L) INHIBIT?)
L15           86 SEA ABB=ON  PLU=ON  L14 AND (PY<2005 OR AY<2005 OR PRY<2005)
L16           43 DUP REM L15 (43 DUPLICATES REMOVED)
                    ANSWERS '1-16' FROM FILE HCAPLUS
                    ANSWERS '17-19' FROM FILE MEDLINE
                    ANSWERS '20-31' FROM FILE BIOSIS
                    ANSWERS '32-43' FROM FILE DRUGU
L17           47 SEA ABB=ON  PLU=ON  (L12 OR L16)

     FILE 'STNGUIDE' ENTERED AT 09:48:56 ON 26 MAR 2007
                D QUE L9
                D QUE L17

     FILE 'HCAPLUS, MEDLINE, BIOSIS, DRUGU, WPIX' ENTERED AT 09:49:06 ON 26
     MAR 2007
L18           44 DUP REM L9 L17 (9 DUPLICATES REMOVED)
                    ANSWERS '1-17' FROM FILE HCAPLUS
                    ANSWERS '18-20' FROM FILE MEDLINE
                    ANSWERS '21-32' FROM FILE BIOSIS
                    ANSWERS '33-44' FROM FILE DRUGU
                D IBIB ABS HITSTR RETABLE L18 1-17
                D IBIB ABS L18 18-44

     FILE 'REGISTRY' ENTERED AT 10:03:00 ON 26 MAR 2007
                E BUTANEDIOIC ACID/CNS
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                E ACETYLAMINO/CNS AND CYCLOHEXYLPHENYL/CNS

     FILE 'STNGUIDE' ENTERED AT 10:06:18 ON 26 MAR 2007

     FILE 'REGISTRY' ENTERED AT 10:13:17 ON 26 MAR 2007
L19               STRUCTURE UPLOADED
L20               STRUCTURE UPLOADED
L21               STRUCTURE UPLOADED
L22               STRUCTURE UPLOADED
L23             0 SEA SSS SAM L19
L24             0 SEA SSS SAM L20
L25             0 SEA SSS SAM L21
L26             0 SEA SSS SAM L22
L27             1 SEA SSS FUL L19
                  D SCAN
L28             1 SEA SSS FUL L20
                  D SCAN
L29             2 SEA SSS FUL L21
                  D SCAN
L30             4 SEA SSS FUL L22
                  D SCAN
                  D SCAN L27
                  D BROW L27
L31             0 SEA ABB=ON  PLU=ON  38913-13-2/CRN
                  D BROW L28
L32             0 SEA ABB=ON  PLU=ON  38913-20-1/CRN
                  D BROW L29
L33             1 SEA ABB=ON  PLU=ON  66123-61-3
L34             0 SEA ABB=ON  PLU=ON  66123-61-3/CRN
                  D BROW L30
                  D RN L30 1-4
L35             0 SEA ABB=ON  PLU=ON  117726-66-6/CRN
L36             0 SEA ABB=ON  PLU=ON  103271-91-6/CRN
L37             0 SEA ABB=ON  PLU=ON  66123-61-3/CRN
L38             0 SEA ABB=ON  PLU=ON  66123-34-0/CRN
                  D SCAN L27
                  E BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]-/CN
                  D BROW L27
                  E BUTANEDIOIC ACID, [3-(ACETYLAMINO)-4-CYCLOHEXYLPHENYL]/CN

     FILE 'HCAPLUS' ENTERED AT 10:21:02 ON 26 MAR 2007
L39             1 SEA ABB=ON  PLU=ON  L27
L40             1 SEA ABB=ON  PLU=ON  L28
L41             1 SEA ABB=ON  PLU=ON  L33
L42             3 SEA ABB=ON  PLU=ON  L30
L43             4 SEA ABB=ON  PLU=ON  (L39 OR L40 OR L41 OR L42)
                  D BIB TOT

     FILE 'REGISTRY' ENTERED AT 10:21:42 ON 26 MAR 2007
L44             6 SEA ABB=ON  PLU=ON  (L27 OR L28 OR L33 OR L30)
                  D BROW

     FILE 'HCAPLUS' ENTERED AT 10:22:32 ON 26 MAR 2007
L45             0 SEA ABB=ON  PLU=ON  L43 AND METALLOPROTEINASE?

     FILE 'BEILSTEIN' ENTERED AT 10:23:16 ON 26 MAR 2007
L46             1 SEA SSS FUL L19
L47             1 SEA SSS FUL L20
L48             0 SEA SSS FUL L21
L49             1 SEA SSS FUL L22
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